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(54) Title: NOVEL COMPOUNDS

(57) Abstract: Polypeptides and polynucleotides of the genes set forth in Table I and methods for producing such polypeptides by recombinant techniques are disclosed. Also disclosed are methods for utilizing polypeptides and polynucleotides of the genes set forth in Table I in diagnostic assays.

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Novel Compounds

Field of Invention

This invention relates to newly identified polypeptides and polynucleotides encoding such polypeptides, to their use in diagnosis and in identifying compounds that may be agonists, antagonists that are potentially useful in therapy, and to production of such polypeptides and polynucleotides. The polynucleotides and polypeptides of the present invention also relate to proteins with signal sequences which allow them to be secreted extracellularly or membrane-associated (hereinafter often referred collectively as secreted proteins or secreted polypeptides).

Background of the Invention

The drug discovery process is currently undergoing a fundamental revolution as it embraces "functional genomics", that is, high throughput genome- or gene-based biology. This approach as a means to identify genes and gene products as therapeutic targets is rapidly superseding earlier approaches based on "positional cloning". A phenotype, that is a biological function or genetic disease, would be identified and this would then be tracked back to the responsible gene, based on its genetic map position.

Functional genomics relies heavily on high-throughput DNA sequencing technologies and the various tools of bioinformatics to identify gene sequences of potential interest from the many molecular biology databases now available. There is a continuing need to identify and characterise further genes and their related polypeptides/proteins, as targets for drug discovery.

Proteins and polypeptides that are naturally secreted into blood, lymph and other body fluids, or secreted into the cellular membrane are of primary interest for pharmaceutical research and development. The reason for this interest is the relative ease to target protein therapeutics into their place of action (body fluids or the cellular membrane). The natural pathway for protein secretion into extracellular space is the endoplasmic reticulum in eukaryotes and the inner membrane in prokaryotes (Palade, 1975, Science, 189, 347; Milstein, Brownlee, Harrison, and Mathews, 1972, Nature New Biol., 239, 117; Blobel, and Dobberstein, 1975, J. Cell. Biol., 67, 835). On the other hand, there is no known natural pathway for exporting a protein from the exterior of the cells into the cytosol (with the exception of pinocytosis, a mechanism of snake venom toxin intrusion into cells). Therefore targeting protein therapeutics into cells poses extreme difficulties.

The secreted and membrane-associated proteins include but are not limited to all peptide hormones and their receptors (including but not limited to insulin, growth hormones, chemokines, cytokines, neuropeptides, integrins, kallikreins, lamins,

melanins, natriuretic hormones, neuropsin, neurotropins, pituitiary hormones, pleiotropins, prostaglandins, secretogranins, selectins, thromboglobulins, thymosins), the breast and colon cancer gene products, leptin, the obesity gene protein and its receptors, serum albumin, superoxide dismutase, spliceosome proteins, 7TM (transmembrane) proteins also called as G-protein coupled receptors, immunoglobulins, several families of serine proteinases (including but not limited to proteins of the blood coagulation cascade, digestive enzymes), deoxyribonuclease I, etc.

Therapeutics based on secreted or membrane-associated proteins approved by FDA or foreign agencies include but are not limited to insulin, glucagon, growth hormone, chorionic gonadotropin, follicle stimulating hormone, luteinizing hormone, calcitonin, adrenocorticotropic hormone (ACTH), vasopressin, interleukines, interferones, immunoglobulins, lactoferrin (diverse products marketed by several companies), tissue-type plasminogen activator (Alteplase by Genentech), hyaulorindase (Wydase by Wyeth-Ayerst), dornase alpha (Pulmozyme\ by Genentech), Chymodiactin (chymopapain by Knoll), alglucerase (Ceredase by Genzyme), streptokinase (Kabikinase by Pharmacia) (Streptase by Astra), etc. This indicates that secreted and membrane-associated proteins have an established, proven history as therapeutic targets. Clearly, there is a need for identification and characterization of further secreted and membrane-associated proteins which can play a role in preventing, ameliorating or correcting dysfunction or disease, including but not limited to diabetes, breast-, prostate-, colon cancer and other malignant tumors, hyper- and hypotension, obesity, bulimia, anorexia, growth abnormalities, asthma, manic depression, dementia, delirium, mental retardation, Huntington's disease, Tourette's syndrome, schizophrenia, growth, mental or sexual development disorders, and dysfunctions of the blood cascade system including those leading to stroke. The proteins of the present invention which include the signal sequences are also useful to further elucidate the mechanism of protein transport which at present is not entirely understood, and thus can be used as research tools.

Summary of the Invention

The present invention relates to particular polypeptides and polynucleotides of the genes set forth in Table I, including recombinant materials and methods for their production. Such polypeptides and polynucleotides are of interest in relation to methods of treatment of certain diseases, including, but not limited to, the diseases set forth in Tables III and V,

hereinafter referred to as "diseases of the invention". In a further aspect, the invention relates to methods for identifying agonists and antagonists (*e.g.*, inhibitors) using the materials provided by the invention, and treating conditions associated with imbalance of polypeptides and/or polynucleotides of the genes set forth in Table I with the identified compounds. In still a further aspect, the invention relates to diagnostic assays for detecting diseases associated with inappropriate activity or levels the genes set forth in Table I. Another aspect of the invention concerns a polynucleotide comprising any of the nucleotide sequences set forth in the Sequence Listing and a polypeptide comprising a polypeptide encoded by the nucleotide sequence. In another aspect, the invention relates to a polypeptide comprising any of the polypeptide sequences set forth in the Sequence Listing and recombinant materials and methods for their production. Another aspect of the invention relates to methods for using such polypeptides and polynucleotides. Such uses include the treatment of diseases, abnormalities and disorders (hereinafter simply referred to as diseases) caused by abnormal expression, production, function and or metabolism of the genes of this invention, and such diseases are readily apparent by those skilled in the art from the homology to other proteins disclosed for each attached sequence. In still another aspect, the invention relates to methods to identify agonists and antagonists using the materials provided by the invention, and treating conditions associated with the imbalance with the identified compounds. Yet another aspect of the invention relates to diagnostic assays for detecting diseases associated with inappropriate activity or levels of the secreted proteins of the present invention.

Description of the Invention

In a first aspect, the present invention relates to polypeptides the genes set forth in Table I. Such polypeptides include:

(a) an isolated polypeptide encoded by a polynucleotide comprising a sequence set forth in the Sequence Listing, herein when referring to polynucleotides or polypeptides of the Sequence Listing, a reference is also made to the Sequence Listing referred to in the Sequence Listing;

(b) an isolated polypeptide comprising a polypeptide sequence having at least 95%, 96%, 97%, 98%, or 99% identity to a polypeptide sequence set forth in the Sequence Listing;

(c) an isolated polypeptide comprising a polypeptide sequence set forth in the Sequence Listing;

(d) an isolated polypeptide having at least 95%, 96%, 97%, 98%, or 99% identity to a polypeptide sequence set forth in the Sequence Listing;

(e) a polypeptide sequence set forth in the Sequence Listing; and

(f) an isolated polypeptide having or comprising a polypeptide sequence that has an Identity Index of 0.95, 0.96, 0.97, 0.98, or 0.99 compared to a polypeptide sequence set forth in the Sequence Listing;

(g) fragments and variants of such polypeptides in (a) to (f).

Polypeptides of the present invention are believed to be members of the gene families set forth in Table II . They are therefore of therapeutic and diagnostic interest for the reasons set forth in Tables III and V. The biological properties of the polypeptides and polynucleotides of the genes set forth in Table I are hereinafter referred to as "the biological activity" of polypeptides and polynucleotides of the genes set forth in Table I. Preferably, a polypeptide of the present invention exhibits at least one biological activity of the genes set forth in Table I.

Polypeptides of the present invention also include variants of the aforementioned polypeptides, including all allelic forms and splice variants. Such polypeptides vary from the reference polypeptide by insertions, deletions, and substitutions that may be conservative or non-conservative, or any combination thereof. Particularly preferred variants are those in which several, for instance from 50 to 30, from 30 to 20, from 20 to 10, from 10 to 5, from 5 to 3, from 3 to 2, from 2 to 1 or 1 amino acids are inserted, substituted, or deleted, in any combination.

Preferred fragments of polypeptides of the present invention include an isolated polypeptide comprising an amino acid sequence having at least 30, 50 or 100 contiguous amino acids from an amino acid sequence set forth in the Sequence Listing, or an isolated polypeptide comprising an amino acid sequence having at least 30, 50 or 100 contiguous amino acids truncated or deleted from an amino acid sequence set forth in the Sequence Listing. Preferred fragments are biologically active fragments that mediate the biological activity of polypeptides and polynucleotides of the genes set forth in Table I, including those with a similar activity or an improved activity, or with a decreased undesirable activity. Also preferred are those fragments that are antigenic or immunogenic in an animal, especially in a human.

Fragments of a polypeptide of the invention may be employed for producing the corresponding full-length polypeptide by peptide synthesis; therefore, these variants may be employed as intermediates for producing the full-length polypeptides of the invention. A polypeptide of the present invention may be in the form of the "mature" protein or may be a part of a larger protein such as a precursor or a fusion protein. It is often advantageous to include an additional amino acid sequence that contains secretory or leader sequences, pro-sequences,

sequences that aid in purification, for instance multiple histidine residues, or an additional sequence for stability during recombinant production.

Polypeptides of the present invention can be prepared in any suitable manner, for instance by isolation form naturally occurring sources, from genetically engineered host cells comprising expression systems (*vide infra*) or by chemical synthesis, using for instance automated peptide synthesizers, or a combination of such methods. Means for preparing such polypeptides are well understood in the art.

In a further aspect, the present invention relates to polynucleotides of the genes set forth in Table I. Such polynucleotides include:

(a) an isolated polynucleotide comprising a polynucleotide sequence having at least 95%, 96%, 97%, 98%, or 99% identity to a polynucleotide sequence set forth in the Sequence Listing;

(b) an isolated polynucleotide comprising a polynucleotide set forth in the Sequence Listing;

(c) an isolated polynucleotide having at least 95%, 96%, 97%, 98%, or 99% identity to a polynucleotide set forth in the Sequence Listing;

(d) an isolated polynucleotide set forth in the Sequence Listing;

(e) an isolated polynucleotide comprising a polynucleotide sequence encoding a polypeptide sequence having at least 95%, 96%, 97%, 98%, or 99% identity to a polypeptide sequence set forth in the Sequence Listing;

(f) an isolated polynucleotide comprising a polynucleotide sequence encoding a polypeptide set forth in the Sequence Listing;

(g) an isolated polynucleotide having a polynucleotide sequence encoding a polypeptide sequence having at least 95%, 96%, 97%, 98%, or 99% identity to a polypeptide sequence set forth in the Sequence Listing;

(h) an isolated polynucleotide encoding a polypeptide set forth in the Sequence Listing;

(i) an isolated polynucleotide having or comprising a polynucleotide sequence that has an Identity Index of 0.95, 0.96, 0.97, 0.98, or 0.99 compared to a polynucleotide sequence set forth in the Sequence Listing;

(j) an isolated polynucleotide having or comprising a polynucleotide sequence encoding a polypeptide sequence that has an Identity Index of 0.95, 0.96, 0.97, 0.98, or 0.99 compared to a polypeptide sequence set forth in the Sequence Listing; and

polynucleotides that are fragments and variants of the above mentioned polynucleotides or that are complementary to above mentioned polynucleotides, over the entire length thereof.

Preferred fragments of polynucleotides of the present invention include an isolated polynucleotide comprising an nucleotide sequence having at least 15, 30, 50 or 100 contiguous nucleotides from a sequence set forth in the Sequence Listing, or an isolated polynucleotide comprising a sequence having at least 30, 50 or 100 contiguous nucleotides truncated or deleted from a sequence set forth in the Sequence Listing.

Preferred variants of polynucleotides of the present invention include splice variants, allelic variants, and polymorphisms, including polynucleotides having one or more single nucleotide polymorphisms (SNPs).

Polynucleotides of the present invention also include polynucleotides encoding polypeptide variants that comprise an amino acid sequence set forth in the Sequence Listing and in which several, for instance from 50 to 30, from 30 to 20, from 20 to 10, from 10 to 5, from 5 to 3, from 3 to 2, from 2 to 1 or 1 amino acid residues are substituted, deleted or added, in any combination.

In a further aspect, the present invention provides polynucleotides that are RNA transcripts of the DNA sequences of the present invention. Accordingly, there is provided an RNA polynucleotide that:

(a) comprises an RNA transcript of the DNA sequence encoding a polypeptide set forth in the Sequence Listing;

(b) is a RNA transcript of a DNA sequence encoding a polypeptide set forth in the Sequence Listing;

(c) comprises an RNA transcript of a DNA sequence set forth in the Sequence Listing; or

(d) is a RNA transcript of a DNA sequence set forth in the Sequence Listing;

and RNA polynucleotides that are complementary thereto.

The polynucleotide sequences set forth in the Sequence Listing show homology with the polynucleotide sequences set forth in Table II. A polynucleotide sequence set forth in the Sequence Listing is a cDNA sequence that encodes a polypeptide set forth in the Sequence Listing. A polynucleotide sequence encoding a polypeptide set forth in the Sequence Listing may be identical to a polypeptide encoding a sequence set forth in the Sequence Listing or it may be a sequence other than a sequence set forth in the Sequence Listing, which, as a result of the redundancy (degeneracy) of the genetic code, also encodes a polypeptide set forth in the Sequence Listing. A polypeptide of a sequence set forth in the Sequence Listingis related to

other proteins of the gene families set forth in Table II, having homology and/or structural similarity with the polypeptides set forth in Table II. Preferred polypeptides and polynucleotides of the present invention are expected to have, *inter alia*, similar biological functions/properties to their homologous polypeptides and polynucleotides. Furthermore, preferred polypeptides and polynucleotides of the present invention have at least one activity of the genes set forth in Table I.

Polynucleotides of the present invention may be obtained using standard cloning and screening techniques from a cDNA library derived from mRNA from the tissues set forth in Table IV (see for instance, Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, 2nd Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989)). Polynucleotides of the invention can also be obtained from natural sources such as genomic DNA libraries or can be synthesized using well known and commercially available techniques.

When polynucleotides of the present invention are used for the recombinant production of polypeptides of the present invention, the polynucleotide may include the coding sequence for the mature polypeptide, by itself, or the coding sequence for the mature polypeptide in reading frame with other coding sequences, such as those encoding a leader or secretory sequence, a pre-, or pro- or prepro- protein sequence, or other fusion peptide portions. For example, a marker sequence that facilitates purification of the fused polypeptide can be encoded. In certain preferred embodiments of this aspect of the invention, the marker sequence is a hexa-histidine peptide, as provided in the pQE vector (Qiagen, Inc.) and described in Gentz *et al.*, Proc Natl Acad Sci USA (1989) 86:821-824, or is an HA tag. A polynucleotide may also contain non-coding 5' and 3' sequences, such as transcribed, non-translated sequences, splicing and polyadenylation signals, ribosome binding sites and sequences that stabilize mRNA.

Polynucleotides that are identical, or have sufficient identity to a polynucleotide sequence set forth in the Sequence Listing, may be used as hybridization probes for cDNA and genomic DNA or as primers for a nucleic acid amplification reaction (for instance, PCR). Such probes and primers may be used to isolate full-length cDNAs and genomic clones encoding polypeptides of the present invention and to isolate cDNA and genomic clones of other genes (including genes encoding paralogs from human sources and orthologs and paralogs from species other than) that have a high sequence similarity to sequences set forth in the Sequence Listing, typically at least 95% identity. Preferred probes and primers will generally comprise at least 15 nucleotides, preferably, at least 30 nucleotides and may have at least 50, if not at least

100 nucleotides. Particularly preferred probes will have between 30 and 50 nucleotides. Particularly preferred primers will have between 20 and 25 nucleotides.

A polynucleotide encoding a polypeptide of the present invention, including homologs from species other than , may be obtained by a process comprising the steps of screening a library under stringent hybridization conditions with a labeled probe having a sequence set forth in the Sequence Listing or a fragment thereof, preferably of at least 15 nucleotides; and isolating full-length cDNA and genomic clones containing the polynucleotide sequence set forth in the Sequence Listing. Such hybridization techniques are well known to the skilled artisan. Preferred stringent hybridization conditions include overnight incubation at 42°C in a solution comprising: 50% formamide, 5xSSC (150mM NaCl, 15mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10 % dextran sulfate, and 20 microgram/ml denatured, sheared salmon sperm DNA; followed by washing the filters in 0.1x SSC at about 65°C. Thus the present invention also includes isolated polynucleotides, preferably with a nucleotide sequence of at least 100, obtained by screening a library under stringent hybridization conditions with a labeled probe having the sequence set forth in the Sequence Listing or a fragment thereof, preferably of at least 15 nucleotides.

The skilled artisan will appreciate that, in many cases, an isolated cDNA sequence will be incomplete, in that the region coding for the polypeptide does not extend all the way through to the 5' terminus. This is a consequence of reverse transcriptase, an enzyme with inherently low "processivity" (a measure of the ability of the enzyme to remain attached to the template during the polymerisation reaction), failing to complete a DNA copy of the mRNA template during first strand cDNA synthesis.

There are several methods available and well known to those skilled in the art to obtain full-length cDNAs, or extend short cDNAs, for example those based on the method of Rapid Amplification of cDNA ends (RACE) (see, for example, Frohman et al., Proc Nat Acad Sci USA 85, 8998-9002, 1988). Recent modifications of the technique, exemplified by the Marathon (trade mark) technology (Clontech Laboratories Inc.) for example, have significantly simplified the search for longer cDNAs. In the Marathon (trade mark) technology, cDNAs have been prepared from mRNA extracted from a chosen tissue and an 'adaptor' sequence ligated onto each end. Nucleic acid amplification (PCR) is then carried out to amplify the "missing" 5' end of the cDNA using a combination of gene specific and adaptor specific oligonucleotide primers. The PCR reaction is then repeated using 'nested' primers, that is, primers designed to

anneal within the amplified product (typically an adapter specific primer that anneals further 3' in the adaptor sequence and a gene specific primer that anneals further 5' in the known gene sequence). The products of this reaction can then be analyzed by DNA sequencing and a full-length cDNA constructed either by joining the product directly to the existing cDNA to give a complete sequence, or carrying out a separate full-length PCR using the new sequence information for the design of the 5' primer.

Recombinant polypeptides of the present invention may be prepared by processes well known in the art from genetically engineered host cells comprising expression systems. Accordingly, in a further aspect, the present invention relates to expression systems comprising a polynucleotide or polynucleotides of the present invention, to host cells which are genetically engineered with such expression systems and to the production of polypeptides of the invention by recombinant techniques. Cell-free translation systems can also be employed to produce such proteins using RNAs derived from the DNA constructs of the present invention.

For recombinant production, host cells can be genetically engineered to incorporate expression systems or portions thereof for polynucleotides of the present invention. Polynucleotides may be introduced into host cells by methods described in many standard laboratory manuals, such as Davis et al., Basic Methods in Molecular Biology (1986) and Sambrook *et al.*(*ibid*). Preferred methods of introducing polynucleotides into host cells include, for instance, calcium phosphate transfection, DEAE-dextran mediated transfection, transvection, micro-injection, cationic lipid-mediated transfection, electroporation, transduction, scrape loading, ballistic introduction or infection.

Representative examples of appropriate hosts include bacterial cells, such as *Streptococci*, *Staphylococci*, *E. coli*, *Streptomyces* and *Bacillus subtilis* cells; fungal cells, such as yeast cells and *Aspergillus* cells; insect cells such as *Drosophila* S2 and *Spodoptera* Sf9 cells; animal cells such as CHO, COS, HeLa, C127, 3T3, BHK, HEK 293 and Bowes melanoma cells; and plant cells.

A great variety of expression systems can be used, for instance, chromosomal, episomal and virus-derived systems, *e.g.*, vectors derived from bacterial plasmids, from bacteriophage, from transposons, from yeast episomes, from insertion elements, from yeast chromosomal elements, from viruses such as baculoviruses, papova viruses, such as SV40, vaccinia viruses, adenoviruses, fowl pox viruses, pseudorabies viruses and retroviruses, and vectors derived from combinations thereof, such as those derived from plasmid and bacteriophage genetic elements,

such as cosmids and phagemids. The expression systems may contain control regions that regulate as well as engender expression. Generally, any system or vector that is able to maintain, propagate or express a polynucleotide to produce a polypeptide in a host may be used. The appropriate polynucleotide sequence may be inserted into an expression system by any of a variety of well-known and routine techniques, such as, for example, those set forth in Sambrook *et al.*, (*ibid*). Appropriate secretion signals may be incorporated into the desired polypeptide to allow secretion of the translated protein into the lumen of the endoplasmic reticulum, the periplasmic space or the extracellular environment. These signals may be endogenous to the polypeptide or they may be heterologous signals.

If a polypeptide of the present invention is to be expressed for use in screening assays, it is generally preferred that the polypeptide be produced at the surface of the cell. In this event, the cells may be harvested prior to use in the screening assay. If the polypeptide is secreted into the medium, the medium can be recovered in order to recover and purify the polypeptide. If produced intracellularly, the cells must first be lysed before the polypeptide is recovered.

Polypeptides of the present invention can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography is employed for purification. Well known techniques for refolding proteins may be employed to regenerate active conformation when the polypeptide is denatured during intracellular synthesis, isolation and/or purification.

Polynucleotides of the present invention may be used as diagnostic reagents, through detecting mutations in the associated gene. Detection of a mutated form of a gene is characterized by the polynucleotides set forth in the Sequence Listing in the cDNA or genomic sequence and which is associated with a dysfunction. Will provide a diagnostic tool that can add to, or define, a diagnosis of a disease, or susceptibility to a disease, which results from under-expression, over-expression or altered spatial or temporal expression of the gene. Individuals carrying mutations in the gene may be detected at the DNA level by a variety of techniques well known in the art.

Nucleic acids for diagnosis may be obtained from a subject's cells, such as from blood, urine, saliva, tissue biopsy or autopsy material. The genomic DNA may be used directly for

detection or it may be amplified enzymatically by using PCR, preferably RT-PCR, or other amplification techniques prior to analysis. RNA or cDNA may also be used in similar fashion. Deletions and insertions can be detected by a change in size of the amplified product in comparison to the normal genotype. Point mutations can be identified by hybridizing amplified DNA to labeled nucleotide sequences of the genes set forth in Table I. Perfectly matched sequences can be distinguished from mismatched duplexes by RNase digestion or by differences in melting temperatures. DNA sequence difference may also be detected by alterations in the electrophoretic mobility of DNA fragments in gels, with or without denaturing agents, or by direct DNA sequencing (see, for instance, Myers *et al.*, Science (1985) 230:1242). Sequence changes at specific locations may also be revealed by nuclease protection assays, such as RNase and S1 protection or the chemical cleavage method (see Cotton *et al.*, Proc Natl Acad Sci USA (1985) 85: 4397-4401).

An array of oligonucleotides probes comprising polynucleotide sequences or fragments thereof of the genes set forth in Table I can be constructed to conduct efficient screening of *e.g.*, genetic mutations. Such arrays are preferably high density arrays or grids. Array technology methods are well known and have general applicability and can be used to address a variety of questions in molecular genetics including gene expression, genetic linkage, and genetic variability, see, for example, M. Chee et al., Science, 274, 610-613 (1996) and other references cited therein.

Detection of abnormally decreased or increased levels of polypeptide or mRNA expression may also be used for diagnosing or determining susceptibility of a subject to a disease of the invention. Decreased or increased expression can be measured at the RNA level using any of the methods well known in the art for the quantitation of polynucleotides, such as, for example, nucleic acid amplification, for instance PCR, RT-PCR, RNase protection, Northern blotting and other hybridization methods. Assay techniques that can be used to determine levels of a protein, such as a polypeptide of the present invention, in a sample derived from a host are well-known to those of skill in the art. Such assay methods include radio-immunoassays, competitive-binding assays, Western Blot analysis and ELISA assays.

Thus in another aspect, the present invention relates to a diagnostic kit comprising:

(a) a polynucleotide of the present invention, preferably the nucleotide sequence set forth in the Sequence Listing , or a fragment or an RNA transcript thereof;

(b) a nucleotide sequence complementary to that of (a);

(c) a polypeptide of the present invention, preferably the polypeptide set forth in the Sequence Listing or a fragment thereof; or

(d) an antibody to a polypeptide of the present invention, preferably to the polypeptide set forth in the Sequence Listing .

It will be appreciated that in any such kit, (a), (b), (c) or (d) may comprise a substantial component. Such a kit will be of use in diagnosing a disease or susceptibility to a disease, particularly diseases of the invention, amongst others.

The polynucleotide.sequences of the present invention are valuable for chromosome localisation studies. The sequences set forth in the Sequence Listing are specifically targeted to, and can hybridize with, a particular location on an individual human chromosome. The mapping of relevant sequences to chromosomes according to the present invention is an important first step in correlating those sequences with gene associated disease. Once a sequence has been mapped to a precise chromosomal location, the physical position of the sequence on the chromosome can be correlated with genetic map data. Such data are found in, for example, V. McKusick, Mendelian Inheritance in Man (available on-line through Johns Hopkins University Welch Medical Library). The relationship between genes and diseases that have been mapped to the same chromosomal region are then identified through linkage analysis (co-inheritance of physically adjacent genes). Precise human chromosomal localisations for a genomic sequence (gene fragment etc.) can be determined using Radiation Hybrid (RH) Mapping (Walter, M. Spillett, D., Thomas, P., Weissenbach, J., and Goodfellow, P., (1994) A method for constructing radiation hybrid maps of whole genomes, Nature Genetics 7, 22-28). A number of RH panels are available from Research Genetics (Huntsville, AL, USA) e.g. the GeneBridge4 RH panel (Hum Mol Genet 1996 Mar;5(3):339-46 A radiation hybrid map of the human genome. Gyapay G, Schmitt K, Fizames C, Jones H, Vega-Czarny N, Spillett D, Muselet D, Prud'Homme JF, Dib C, Auffray C, Morissette J, Weissenbach J, Goodfellow PN). To determine the chromosomal location of a gene using this panel, 93 PCRs are performed using primers designed from the gene of interest on RH DNAs. Each of these DNAs contains random human genomic fragments maintained in a hamster background (human / hamster hybrid cell lines). These PCRs result in 93 scores indicating the presence or absence of the PCR product of the gene of interest. These scores are compared with scores created using PCR products from genomic sequences of known location. This comparison is conducted at http://www.genome.wi.mit.edu/.

The polynucleotide sequences of the present invention are also valuable tools for tissue expression studies. Such studies allow the determination of expression patterns of polynucleotides of the present invention which may give an indication as to the expression patterns of the encoded polypeptides in tissues, by detecting the mRNAs that encode them. The techniques used are well known in the art and include in situ hydridization techniques to clones arrayed on a grid, such as cDNA microarray hybridization (Schena *et al*, Science, 270, 467-470, 1995 and Shalon *et al*, Genome Res, 6, 639-645, 1996) and nucleotide amplification techniques such as PCR. A preferred method uses the TAQMAN (Trade mark) technology available from Perkin Elmer. Results from these studies can provide an indication of the normal function of the polypeptide in the organism. In addition, comparative studies of the normal expression pattern of mRNAs with that of mRNAs encoded by an alternative form of the same gene (for example, one having an alteration in polypeptide coding potential or a regulatory mutation) can provide valuable insights into the role of the polypeptides of the present invention, or that of inappropriate expression thereof in disease. Such inappropriate expression may be of a temporal, spatial or simply quantitative nature.

A further aspect of the present invention relates to antibodies. The polypeptides of the invention or their fragments, or cells expressing them, can be used as immunogens to produce antibodies that are immunospecific for polypeptides of the present invention. The term "immunospecific" means that the antibodies have substantially greater affinity for the polypeptides of the invention than their affinity for other related polypeptides in the prior art.

Antibodies generated against polypeptides of the present invention may be obtained by administering the polypeptides or epitope-bearing fragments, or cells to an animal, preferably a non-human animal, using routine protocols. For preparation of monoclonal antibodies, any technique which provides antibodies produced by continuous cell line cultures can be used. Examples include the hybridoma technique (Kohler, G. and Milstein, C., Nature (1975) 256:495-497), the trioma technique, the human B-cell hybridoma technique (Kozbor *et al.*, Immunology Today (1983) 4:72) and the EBV-hybridoma technique (Cole *et al.*, Monoclonal Antibodies and Cancer Therapy, 77-96, Alan R. Liss, Inc., 1985).

Techniques for the production of single chain antibodies, such as those described in U.S. Patent No. 4,946,778, can also be adapted to produce single chain antibodies to polypeptides of this invention. Also, transgenic mice, or other organisms, including other mammals, may be used to express humanized antibodies.

The above-described antibodies may be employed to isolate or to identify clones expressing the polypeptide or to purify the polypeptides by affinity chromatography. Antibodies against polypeptides of the present invention may also be employed to treat diseases of the invention, amongst others.

Polypeptides and polynucleotides of the present invention may also be used as vaccines. Accordingly, in a further aspect, the present invention relates to a method for inducing an immunological response in a mammal that comprises inoculating the mammal with a polypeptide of the present invention, adequate to produce antibody and/or T cell immune response, including, for example, cytokine-producing T cells or cytotoxic T cells, to protect said animal from disease, whether that disease is already established within the individual or not. An immunological response in a mammal may also be induced by a method comprises delivering a polypeptide of the present invention *via* a vector directing expression of the polynucleotide and coding for the polypeptide *in vivo* in order to induce such an immunological response to produce antibody to protect said animal from diseases of the invention. One way of administering the vector is by accelerating it into the desired cells as a coating on particles or otherwise. Such nucleic acid vector may comprise DNA, RNA, a modified nucleic acid, or a DNA/RNA hybrid. For use a vaccine, a polypeptide or a nucleic acid vector will be normally provided as a vaccine formulation (composition). The formulation may further comprise a suitable carrier. Since a polypeptide may be broken down in the stomach, it is preferably administered parenterally (for instance, subcutaneous, intra-muscular, intravenous, or intra-dermal injection). Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions that may contain anti-oxidants, buffers, bacteriostats and solutes that render the formulation instonic with the blood of the recipient; and aqueous and non-aqueous sterile suspensions that may include suspending agents or thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed ampoules and vials and may be stored in a freeze-dried condition requiring only the addition of the sterile liquid carrier immediately prior to use. The vaccine formulation may also include adjuvant systems for enhancing the immunogenicity of the formulation, such as oil-in water systems and other systems known in the art. The dosage will depend on the specific activity of the vaccine and can be readily determined by routine experimentation.

Polypeptides of the present invention have one or more biological functions that are of relevance in one or more disease states, in particular the diseases of the invention hereinbefore

mentioned. It is therefore useful to identify compounds that stimulate or inhibit the function or level of the polypeptide. Accordingly, in a further aspect, the present invention provides for a method of screening compounds to identify those that stimulate or inhibit the function or level of the polypeptide. Such methods identify agonists or antagonists that may be employed for therapeutic and prophylactic purposes for such diseases of the invention as hereinbefore mentioned. Compounds may be identified from a variety of sources, for example, cells, cell-free preparations, chemical libraries, collections of chemical compounds, and natural product mixtures. Such agonists or antagonists so-identified may be natural or modified substrates, ligands, receptors, enzymes, etc., as the case may be, of the polypeptide; a structural or functional mimetic thereof (see Coligan *et al.*, Current Protocols in Immunology 1(2):Chapter 5 (1991)) or a small molecule. Such small molecules preferably have a molecular weight below 2,000 daltons, more preferably between 300 and 1,000 daltons, and most preferably between 400 and 700 daltons. It is preferred that these small molecules are organic molecules.

The screening method may simply measure the binding of a candidate compound to the polypeptide, or to cells or membranes bearing the polypeptide, or a fusion protein thereof, by means of a label directly or indirectly associated with the candidate compound. Alternatively, the screening method may involve measuring or detecting (qualitatively or quantitatively) the competitive binding of a candidate compound to the polypeptide against a labeled competitor (*e.g.* agonist or antagonist). Further, these screening methods may test whether the candidate compound results in a signal generated by activation or inhibition of the polypeptide, using detection systems appropriate to the cells bearing the polypeptide. Inhibitors of activation are generally assayed in the presence of a known agonist and the effect on activation by the agonist by the presence of the candidate compound is observed. Further, the screening methods may simply comprise the steps of mixing a candidate compound with a solution containing a polypeptide of the present invention, to form a mixture, measuring an activity of the genes set forth in Table I in the mixture, and comparing activity of the mixture of the genes set forth in Table I to a control mixture which contains no candidate compound.

Polypeptides of the present invention may be employed in conventional low capacity screening methods and also in high-throughput screening (HTS) formats. Such HTS formats include not only the well-established use of 96- and, more recently, 384-well micotiter plates but also emerging methods such as the nanowell method described by Schullek et al, Anal Biochem., 246, 20-29, (1997).

Fusion proteins, such as those made from Fc portion and polypeptide of the genes set forth in Table I, as hereinbefore described, can also be used for high-throughput screening assays to identify antagonists for the polypeptide of the present invention (see D. Bennett *et al.*, J Mol Recognition, 8:52-58 (1995); and K. Johanson *et al.*, J Biol Chem, 270(16):9459-9471 (1995)).

The polynucleotides, polypeptides and antibodies to the polypeptide of the present invention may also be used to configure screening methods for detecting the effect of added compounds on the production of mRNA and polypeptide in cells. For example, an ELISA assay may be constructed for measuring secreted or cell associated levels of polypeptide using monoclonal and polyclonal antibodies by standard methods known in the art. This can be used to discover agents that may inhibit or enhance the production of polypeptide (also called antagonist or agonist, respectively) from suitably manipulated cells or tissues.

A polypeptide of the present invention may be used to identify membrane bound or soluble receptors, if any, through standard receptor binding techniques known in the art. These include, but are not limited to, ligand binding and crosslinking assays in which the polypeptide is labeled with a radioactive isotope (for instance, ^{125}I), chemically modified (for instance, biotinylated), or fused to a peptide sequence suitable for detection or purification, and incubated with a source of the putative receptor (cells, cell membranes, cell supernatants, tissue extracts, bodily fluids). Other methods include biophysical techniques such as surface plasmon resonance and spectroscopy. These screening methods may also be used to identify agonists and antagonists of the polypeptide that compete with the binding of the polypeptide to its receptors, if any. Standard methods for conducting such assays are well understood in the art.

Examples of antagonists of polypeptides of the present invention include antibodies or, in some cases, oligonucleotides or proteins that are closely related to the ligands, substrates, receptors, enzymes, etc., as the case may be, of the polypeptide, *e.g.*, a fragment of the ligands, substrates, receptors, enzymes, etc.; or a small molecule that bind to the polypeptide of the present invention but do not elicit a response, so that the activity of the polypeptide is prevented.

Screening methods may also involve the use of transgenic technology and the genes set forth in Table I. The art of constructing transgenic animals is well established. For example, the genes set forth in Table I may be introduced through microinjection into the male pronucleus of fertilized oocytes, retroviral transfer into pre- or post-implantation embryos, or injection of genetically modified, such as by electroporation, embryonic stem cells into host

blastocysts. Particularly useful transgenic animals are so-called "knock-in" animals in which an animal gene is replaced by the human equivalent within the genome of that animal. Knock-in transgenic animals are useful in the drug discovery process, for target validation, where the compound is specific for the human target. Other useful transgenic animals are so-called "knock-out" animals in which the expression of the animal ortholog of a polypeptide of the present invention and encoded by an endogenous DNA sequence in a cell is partially or completely annulled. The gene knock-out may be targeted to specific cells or tissues, may occur only in certain cells or tissues as a consequence of the limitations of the technology, or may occur in all, or substantially all, cells in the animal. Transgenic animal technology also offers a whole animal expression-cloning system in which introduced genes are expressed to give large amounts of polypeptides of the present invention

Screening kits for use in the above described methods form a further aspect of the present invention. Such screening kits comprise:

(a) a polypeptide of the present invention;

(b) a recombinant cell expressing a polypeptide of the present invention;

(c) a cell membrane expressing a polypeptide of the present invention; or

(d) an antibody to a polypeptide of the present invention;

which polypeptide is preferably that set forth in the Sequence Listing.

It will be appreciated that in any such kit, (a), (b), (c) or (d) may comprise a substantial component.

Glossary

The following definitions are provided to facilitate understanding of certain terms used frequently hereinbefore.

"Antibodies" as used herein includes polyclonal and monoclonal antibodies, chimeric, single chain, and humanized antibodies, as well as Fab fragments, including the products of an Fab or other immunoglobulin expression library.

"Isolated" means altered "by the hand of man" from its natural state, *i.e.*, if it occurs in nature, it has been changed or removed from its original environment, or both. For example, a polynucleotide or a polypeptide naturally present in a living organism is not "isolated," but the same polynucleotide or polypeptide separated from the coexisting materials of its natural state is "isolated", as the term is employed herein. Moreover, a polynucleotide or polypeptide that is introduced into an organism by transformation, genetic manipulation or by any other

recombinant method is "isolated" even if it is still present in said organism, which organism may be living or non-living.

"Secreted protein activity or secreted polypeptide activity" or "biological activity of the secreted protein or secreted polypeptide" refers to the metabolic or physiologic function of said secreted protein including similar activities or improved activities or these activities with decreased undesirable side-effects. Also included are antigenic and immunogenic activities of said secreted protein.

"Secreted protein gene" refers to a polynucleotide comprising any of the attached nucleotide sequences or allelic variants thereof and/or their complements.

"Polynucleotide" generally refers to any polyribonucleotide (RNA) or polydeoxribonucleotide (DNA), which may be unmodified or modified RNA or DNA. "Polynucleotides" include, without limitation, single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, "polynucleotide" refers to triple-stranded regions comprising RNA or DNA or both RNA and DNA. The term "polynucleotide" also includes DNAs or RNAs containing one or more modified bases and DNAs or RNAs with backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications may be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically or metabolically modified forms of polynucleotides as typically found in nature, as well as the chemical forms of DNA and RNA characteristic of viruses and cells. "Polynucleotide" also embraces relatively short polynucleotides, often referred to as oligonucleotides.

"Polypeptide" refers to any polypeptide comprising two or more amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres. "Polypeptide" refers to both short chains, commonly referred to as peptides, oligopeptides or oligomers, and to longer chains, generally referred to as proteins. Polypeptides may contain amino acids other than the 20 gene-encoded amino acids. "Polypeptides" include amino acid sequences modified either by natural processes, such as post-translational processing, or by chemical modification techniques that are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature. Modifications

may occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present to the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications. Polypeptides may be branched as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched and branched cyclic polypeptides may result from post-translation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, biotinylation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphotidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cystine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination (see, for instance, Proteins - Structure and Molecular Properties, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York, 1993; Wold, F., Post-translational Protein Modifications: Perspectives and Prospects, 1-12, in Post-translational Covalent Modification of Proteins, B. C. Johnson, Ed., Academic Press, New York, 1983; Seifter *et al.*, "Analysis for protein modifications and nonprotein cofactors", Meth Enzymol, 182, 626-646, 1990, and Rattan *et al.*, "Protein Synthesis: Post-translational Modifications and Aging", Ann NY Acad Sci, 663, 48-62, 1992).

"Fragment" of a polypeptide sequence refers to a polypeptide sequence that is shorter than the reference sequence but that retains essentially the same biological function or activity as the reference polypeptide. "Fragment" of a polynucleotide sequence refers to a polynucleotide sequence that is shorter than the reference sequence set forth in the Sequence Listing.

"Variant" refers to a polynucleotide or polypeptide that differs from a reference polynucleotide or polypeptide, but retains the essential properties thereof. A typical variant of a polynucleotide differs in nucleotide sequence from the reference polynucleotide. Changes in the nucleotide sequence of the variant may or may not alter the amino acid sequence of a polypeptide encoded by the reference polynucleotide. Nucleotide changes may result in amino

acid substitutions, additions, deletions, fusions and truncations in the polypeptide encoded by the reference sequence, as discussed below. A typical variant of a polypeptide differs in amino acid sequence from the reference polypeptide. Generally, alterations are limited so that the sequences of the reference polypeptide and the variant are closely similar overall and, in many regions, identical. A variant and reference polypeptide may differ in amino acid sequence by one or more substitutions, insertions, deletions in any combination. A substituted or inserted amino acid residue may or may not be one encoded by the genetic code. Typical conservative substitutions include Gly, Ala; Val, Ile, Leu; Asp, Glu; Asn, Gln; Ser, Thr; Lys, Arg; and Phe and Tyr. A variant of a polynucleotide or polypeptide may be naturally occurring such as an allele, or it may be a variant that is not known to occur naturally. Non-naturally occurring variants of polynucleotides and polypeptides may be made by mutagenesis techniques or by direct synthesis. Also included as variants are polypeptides having one or more post-translational modifications, for instance glycosylation, phosphorylation, methylation, ADP ribosylation and the like. Embodiments include methylation of the N-terminal amino acid, phosphorylations of serines and threonines and modification of C-terminal glycines.

"Allele" refers to one of two or more alternative forms of a gene occurring at a given locus in the genome.

"Polymorphism" refers to a variation in nucleotide sequence (and encoded polypeptide sequence, if relevant) at a given position in the genome within a population.

"Single Nucleotide Polymorphism" (SNP) refers to the occurrence of nucleotide variability at a single nucleotide position in the genome, within a population. An SNP may occur within a gene or within intergenic regions of the genome. SNPs can be assayed using Allele Specific Amplification (ASA). For the process at least 3 primers are required. A common primer is used in reverse complement to the polymorphism being assayed. This common primer can be between 50 and 1500 bps from the polymorphic base. The other two (or more) primers are identical to each other except that the final 3' base wobbles to match one of the two (or more) alleles that make up the polymorphism. Two (or more) PCR reactions are then conducted on sample DNA, each using the common primer and one of the Allele Specific Primers.

"Splice Variant" as used herein refers to cDNA molecules produced from RNA molecules initially transcribed from the same genomic DNA sequence but which have undergone alternative RNA splicing. Alternative RNA splicing occurs when a primary RNA

transcript undergoes splicing, generally for the removal of introns, which results in the production of more than one mRNA molecule each of that may encode different amino acid sequences. The term splice variant also refers to the proteins encoded by the above cDNA molecules.

"Identity" reflects a relationship between two or more polypeptide sequences or two or more polynucleotide sequences, determined by comparing the sequences. In general, identity refers to an exact nucleotide to nucleotide or amino acid to amino acid correspondence of the two polynucleotide or two polypeptide sequences, respectively, over the length of the sequences being compared.

"% Identity" - For sequences where there is not an exact correspondence, a "% identity" may be determined. In general, the two sequences to be compared are aligned to give a maximum correlation between the sequences. This may include inserting "gaps" in either one or both sequences, to enhance the degree of alignment. A % identity may be determined over the whole length of each of the sequences being compared (so-called global alignment), that is particularly suitable for sequences of the same or very similar length, or over shorter, defined lengths (so-called local alignment), that is more suitable for sequences of unequal length.

"Similarity" is a further, more sophisticated measure of the relationship between two polypeptide sequences. In general, "similarity" means a comparison between the amino acids of two polypeptide chains, on a residue by residue basis, taking into account not only exact correspondences between a between pairs of residues, one from each of the sequences being compared (as for identity) but also, where there is not an exact correspondence, whether, on an evolutionary basis, one residue is a likely substitute for the other. This likelihood has an associated "score" from which the "% similarity" of the two sequences can then be determined.

Methods for comparing the identity and similarity of two or more sequences are well known in the art. Thus for instance, programs available in the Wisconsin Sequence Analysis Package, version 9.1 (Devereux J et al, Nucleic Acids Res, 12, 387-395, 1984, available from Genetics Computer Group, Madison, Wisconsin, USA), for example the programs BESTFIT and GAP, may be used to determine the % identity between two polynucleotides and the % identity and the % similarity between two polypeptide sequences. BESTFIT uses the "local homology" algorithm of Smith and Waterman (J Mol Biol, 147,195-197, 1981, Advances in Applied Mathematics, 2, 482-489, 1981) and finds the best single region of similarity between two sequences. BESTFIT is more suited to comparing two polynucleotide or two polypeptide

sequences that are dissimilar in length, the program assuming that the shorter sequence represents a portion of the longer. In comparison, GAP aligns two sequences, finding a "maximum similarity", according to the algorithm of Neddleman and Wunsch (J Mol Biol, 48, 443-453, 1970). GAP is more suited to comparing sequences that are approximately the same length and an alignment is expected over the entire length. Preferably, the parameters "Gap Weight" and "Length Weight" used in each program are 50 and 3, for polynucleotide sequences and 12 and 4 for polypeptide sequences, respectively. Preferably, % identities and similarities are determined when the two sequences being compared are optimally aligned.

Other programs for determining identity and/or similarity between sequences are also known in the art, for instance the BLAST family of programs (Altschul S F et al, J Mol Biol, 215, 403-410, 1990, Altschul S F et al, Nucleic Acids Res., 25:389-3402, 1997, available from the National Center for Biotechnology Information (NCBI), Bethesda, Maryland, USA and accessible through the home page of the NCBI at www.ncbi.nlm.nih.gov) and FASTA (Pearson W R, Methods in Enzymology, 183, 63-99, 1990; Pearson W R and Lipman D J, Proc Nat Acad Sci USA, 85, 2444-2448,1988, available as part of the Wisconsin Sequence Analysis Package).

Preferably, the BLOSUM62 amino acid substitution matrix (Henikoff S and Henikoff J G, Proc. Nat. Acad Sci. USA, 89, 10915-10919, 1992) is used in polypeptide sequence comparisons including where nucleotide sequences are first translated into amino acid sequences before comparison.

Preferably, the program BESTFIT is used to determine the % identity of a query polynucleotide or a polypeptide sequence with respect to a reference polynucleotide or a polypeptide sequence, the query and the reference sequence being optimally aligned and the parameters of the program set at the default value, as hereinbefore described.

"Identity Index" is a measure of sequence relatedness which may be used to compare a candidate sequence (polynucleotide or polypeptide) and a reference sequence. Thus, for instance, a candidate polynucleotide sequence having, for example, an Identity Index of 0.95 compared to a reference polynucleotide sequence is identical to the reference sequence except that the candidate polynucleotide sequence may include on average up to five differences per each 100 nucleotides of the reference sequence. Such differences are selected from the group consisting of at least one nucleotide deletion, substitution, including transition and transversion, or insertion. These differences may occur at the 5' or 3' terminal positions of the reference polynucleotide sequence or anywhere between these terminal positions, interspersed either

individually among the nucleotides in the reference sequence or in one or more contiguous groups within the reference sequence. In other words, to obtain a polynucleotide sequence having an Identity Index of 0.95 compared to a reference polynucleotide sequence, an average of up to 5 in every 100 of the nucleotides of the in the reference sequence may be deleted, substituted or inserted, or any combination thereof, as hereinbefore described. The same applies *mutatis mutandis* for other values of the Identity Index, for instance 0.96, 0.97, 0.98 and 0.99.

Similarly, for a polypeptide, a candidate polypeptide sequence having, for example, an Identity Index of 0.95 compared to a reference polypeptide sequence is identical to the reference sequence except that the polypeptide sequence may include an average of up to five differences per each 100 amino acids of the reference sequence. Such differences are selected from the group consisting of at least one amino acid deletion, substitution, including conservative and non-conservative substitution, or insertion. These differences may occur at the amino- or carboxy-terminal positions of the reference polypeptide sequence or anywhere between these terminal positions, interspersed either individually among the amino acids in the reference sequence or in one or more contiguous groups within the reference sequence. In other words, to obtain a polypeptide sequence having an Identity Index of 0.95 compared to a reference polypeptide sequence, an average of up to 5 in every 100 of the amino acids in the reference sequence may be deleted, substituted or inserted, or any combination thereof, as hereinbefore described. The same applies *mutatis mutandis* for other values of the Identity Index, for instance 0.96, 0.97, 0.98 and 0.99.

The relationship between the number of nucleotide or amino acid differences and the Identity Index may be expressed in the following equation:

$$n_a \leq x_a - (x_a \bullet I),$$

in which:

n_a is the number of nucleotide or amino acid differences,

x_a is the total number of nucleotides or amino acids in a sequence set forth in the Sequence Listing,

I is the Identity Index,

$\bullet$ is the symbol for the multiplication operator, and

in which any non-integer product of x_a and I is rounded down to the nearest integer prior to subtracting it from x_a.

"Homolog" is a generic term used in the art to indicate a polynucleotide or polypeptide sequence possessing a high degree of sequence relatedness to a reference sequence. Such relatedness may be quantified by determining the degree of identity and/or similarity between the two sequences as hereinbefore defined. Falling within this generic term are the terms "ortholog", and "paralog". "Ortholog" refers to a polynucleotide or polypeptide that is the functional equivalent of the polynucleotide or polypeptide in another species. "Paralog" refers to a polynucleotideor polypeptide that within the same species which is functionally similar.

"Fusion protein" refers to a protein encoded by two, often unrelated, fused genes or fragments thereof. In one example, EP-A-0 464 533-A discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, employing an immunoglobulin Fc region as a part of a fusion protein is advantageous for use in therapy and diagnosis resulting in, for example, improved pharmacokinetic properties [see, *e.g.*, EP-A 0232 262]. On the other hand, for some uses it would be desirable to be able to delete the Fc part after the fusion protein has been expressed, detected and purified.

All publications and references, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference in their entirety as if each individual publication or reference were specifically and individually indicated to be incorporated by reference herein as being fully set forth. Any patent application to which this application claims priority is also incorporated by reference herein in its entirety in the manner described above for publications and references.

Table I.

Gene Name	GSK Gene ID	Nucleic Acid SEQ ID NO's	Corresponding Protein SEQ ID NO's
sbg123493SLITa	123493	SEQ ID NO:1	SEQ ID NO:34
sbg14936EGFa	14936	SEQ ID NO:2 SEQ ID NO:3	SEQ ID NO:35 SEQ ID NO:36
SBh80018.cyastin-related	80018	SEQ ID NO:4	SEQ ID NO:37
SBh74552.trypsinogen	74552	SEQ ID NO:5 SEQ ID NO:6	SEQ ID NO:38 SEQ ID NO:39
sbg90060IGFBP	90060	SEQ ID NO:7 SEQ ID NO:8	SEQ ID NO:40 SEQ ID NO:41
sbg97078ANGIOa	97078	SEQ ID NO:9 SEQ ID NO:10	SEQ ID NO:42 SEQ ID NO:43
sbg68091CMP	68091	SEQ ID NO:11 SEQ ID NO:12	SEQ ID NO:44 SEQ ID NO:45
sbg18525LRR	18525	SEQ ID NO:13	SEQ ID NO:46
SBh45597.trypsin inhibitor	45597	SEQ ID NO:14 SEQ ID NO:15	SEQ ID NO:47 SEQ ID NO:48
sbg34640CALa	34640	SEQ ID NO:16 SEQ ID NO:17	SEQ ID NO:49 SEQ ID NO:50
sbg14849LO	14849	SEQ ID NO:18	SEQ ID NO:51
SBh35812.CALGIZZARIN	35812	SEQ ID NO:19 SEQ ID NO:20	SEQ ID NO:52 SEQ ID NO:53
sbg37967ECMPa	37967	SEQ ID NO:21 SEQ ID NO:22	SEQ ID NO:54 SEQ ID NO:55
sbg15037SER	15037	SEQ ID NO:23	SEQ ID NO:56
sbg23161EGFa	23161	SEQ ID NO:24 SEQ ID NO:25	SEQ ID NO:57 SEQ ID NO:58
sbg82008TGFa	82008	SEQ ID NO:26	SEQ ID NO:59
sbg82008TGFb	82008	SEQ ID NO:27	SEQ ID NO:60
sbg27142IGBb	27142	SEQ ID NO:28 SEQ ID NO:29	SEQ ID NO:61 SEQ ID NO:62
sbg239881TAGL	239881	SEQ ID NO:30 SEQ ID NO:31	SEQ ID NO:63 SEQ ID NO:64
sbg248602CHP	248602	SEQ ID NO:32	SEQ ID NO:65
sbg219473HNKS	219473	SEQ ID NO:33	SEQ ID NO:66

Table II

Gene Name	Gene Family	Closest Polynuclotide by homology	Closest Polypeptide by homology	Cell Localization (by homology)
sbg123493S LITa	Slit-like protein	SC:AL157714 Submitted (20-JAN-2001) by Sanger Centre, Hinxton, Cambridgeshire, CB10 1SA, UK.	Rat slit1 protein, gi: 4585574 Brose K, Bland KS, Wang KH, Arnott D, Henzel W, Goodman CS, Tessier-Lavigne M, Kidd T. Cell 1999 Mar 19;96(6):795-806.	Membrane-bound
sbg14936EG Fa	EGF-Like 2 family of polypeptides	GB:Z97832 Submitted (01-FEB-2000) by Sanger Centre, Hinxton, Cambridgeshire, CB10 1SA, UK.	Mouse EGF-related protein SCUBE1, gi: 10998440 Submitted (08-JUN-2000) by Mammalian Genetics Unit, MRC Harwell, Chilton, Didcot, Oxon OX11 0RD, United Kingdom.	Secreted
SBh80018.c yastin-related	Cystatin-related epididymal spermatogeni c protein	GB:AL121894 Submitted (25-OCT-2000) by Sanger Centre, Hinxton, Cambridgeshire, CB10 1SA, UK.	Mouse cystatin T (Zcys3), geneseqp:Y96576 Patented by ZYMOGENETICS INC Patent number and and publication date: WO200031264-A2, 02-JUN-00	Secreted
SBh74552-.trypsinogen	Trypsinogen	GB:U66059 Rowen, L., Koop, B.F. and Hood, L. Science 272 (5269), 1755-1762 (1996).	Mouse Trypsinogen, gi2358070 Rowen,L., Smit,A.F.A. and Hood,L, Submitted (20-JUL-1997) Department of Molecular Biotechnology, Box 357730 University of Washington, Seattle, Washington 98195, USA	Secreted
sbg90060-IGFBP	Insulin-like growth factor binding protein (IGFBP)	GB:AC020916 Direct submitted (12-JAN-2000) by Production Sequencing Facility, DOE Joint Genome Institute, 2800 Mitchell Drive, Walnut Creek, CA 94598, USA	Protein PRO332, geneseqp:Y13396 Patented by Genetech Inc Patent Number and publication date: WO9914328-A2, 25-Mar-99	Secreted

Table II (cont).

Gene Name	Gene Family	Closest Polynuclotide by homology	Closest Polypeptide by homology	Cell Localization (by homology)
sbg97078-ANGIOa	Angiotensin II/vasopressin receptor	GB:AC011476 Direct submitted (07-OCT-1999) by Production Sequencing Facility, DOE Joint Genome Institute, 2800 Mitchell Drive, Walnut Creek, CA 94598, USA.	Human hypothetical protein FLJ20510: gi:8923473. Submitted (02-Nov-2000) by Sumio Sugano, Institute of Medical Science, University of Tokyo, Department of Virology; Shirokane-dai, 4-6-1, Minato-ku, Tokyo 108-8639	Membrane-bound
sbg68091-CMP	Cartilage matrix protein	GB:AC006356 Direct Submitted (29-MAY-1999) byGenome Sequencing Center, Washington University School of Medicine, 4444 Forest Park Parkway, St. Louis, MO 63108, USA	Human zkun5 protein, geneseqp:Y52597. Patented by ZYMOGENETICS INC. Patent number and and publication date: WO9961615-A1, 02-Dec-99	Secreted
sbg18525-LRR	Leucine-rich repeat (LLR)	GB:AC016030 Direct submitted (19-NOV-1999) by Whitehead Institute/MIT Center for Genome Research, 320 Charles Street, Cambridge, MA 02141, USA	Human KIAA0416 protein, gi:7662102. Ishikawa,K., Nagase,T., Nakajima,D., Seki,N., Ohira,M., Miyajima,N., Tanaka,A., Kotani,H., Nomura,N. and Ohara,O. 1997. DNA Res. 4:307-313.	Membrane-bound
SBh45597-.trypsin inhibitor	Rab subfamily of Ras-like GTPase	SC:Z84479 Submitted (16-OCT-1997) by Sanger Centre, Wellcome Trust Genome Campus, Hinxton, Cambridgeshire, CB10 1SA, UK.	Human RAS like GTPASE, gi:3036779. Submitted (16-OCT-1997) Sanger Centre, Wellcome Trust Genome Campus, Hinxton, Cambridgeshire, CB10 1SA, UK.	Cytosolic
sbg34640-CALa	Calgizzarin (endothelial monocyte-activating polypeptide)	GB:AC006483 Sulston,J.E. and Waterston,R Genome Res. 8 (11), 1097-1108 (1998)	Human calgizzarin, gi:1710818. Tanaka,M., Adzuma,K., Iwami,M., Yoshimoto,K., Monden,Y. and Itakura,M. Cancer Lett. 89 (2), 195-200 (1995).	Cytosolic

Table II (cont).

Gene Name	Gene Family	Closest Polynuclotide by homology	Closest Polypeptide by homology	Cell Localization (by homology)
sbg14849LO	Lysyl oxidase-like	GB:AC005033 Direct Submitted (12-JUN-1998) by Genome Sequencing Center, Washington University School of Medicine, 4444 Forest Park Parkway, St. Louis, MO 63108, USA.	Mouse lysyl oxidase-related protein 2, gi:7305239. Jang,W., Hua,A., Spilson,S.V., Miller,W., Roe,B.A. and Meisler,M.H., 1999, Genome Res. 9 : 53-61.	Secreted
SBh35812-.CALGIZ-ZARIN	Calgizzarin (endothelial monocyte-activating polypeptide)	GB:AL133399 Submitted (08-FEB-2000) by Sanger Centre, Hinxton, Cambridgeshire, CB10 1SA, UK.	Mouse calgizzarin, gi:1710819. Submitted (27-NOV-1995) Keith A. Houck, Biomolecular Research, Sphinx Pharmaceuticals Corp., 4615 University Dr., Durham, NC 27707, USA	Cytosolic
sbg37967-ECMPa	Extracellular matrix protein 2	JENA:X57A-X51X57A-X51 found at Jena Genome Sequencing Center	Human extracellular matrix protein 2, gi:4557543. Nishiu,J., Tanaka,T. and Nakamura,Y. Genomics 52, 378-381 (1998)	Secreted
sbg15037-SER	Serine protease	GB:AC005570 Direct submitted (01-SEP-1998) Center for Human Genome Studies, DOE Joint Genome Institute, Los Alamos National Laboratory, MS M888, Los Alamos, NM 87545, USA.	A long isoform of human HELA2 protein, W77297 Patented by Amrad Operations Pty Ltd. Patent number and and publication date: WO9836054-A1, 20-AUG-98	Secreted
sbg23161-EGFa	Extracellular/ epidermal growth factor	GB:Z99756, GB:Z82214 Submitted (08-DEC-1999) by Sanger Centre, Hinxton, Cambridgeshire, CB10 1SA, UK.	Mouse EGF-related protein SCUBE1 gi:10998440. Grimmond,S., Larder,R., Van Hateren,N., Siggers,P., Hulsebos,T.J.M., Arkell,R. and Greenfield, A. Genomics 70 (1), 74-81 (2000)	Secreted
sbg82008-TGFa,b	TGF beta (transforming growth factor beta)	GB:AC008940.frag1. Submitted (03-AUG-1999) by Production Sequencing Facility, DOE Joint Genome Institute, 2800 Mitchell Drive, Walnut Creek, CA 94598, USA	A novel isolated and purified growth factor (GF), Y16714. Patented by UNIV WASHINGTON. Patent number and and publication date: WO9914235, 25-MAR-99	Secreted

Table II (cont).

Gene Name	Gene Family	Closest Polynuclotide by homology	Closest Polypeptide by homology	Cell Localization (by homology)
sbg27142-IGBb	Immunoglobulin superfamily	GB:AC011846: Submitted (15-OCT-1999) Whitehead Institute/MIT Center for Genome Research, 320 Charles Street, Cambridge, MA 02141, USA GB:AC068507: Submitted (03-MAY-2000) Whitehead Institute/MIT Center for Genome Research, 320 Charles Street, Cambridge, MA 02141, USA	Mouse cell adhesion molecule, gi:11862939. Submitted (11-DEC-2000) Junya Toguchida, Kyoto University, Institute for Frontier Medical Sciences; 53 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto, Kyoto 606-8507, Japan	Secreted
sbg239881-TAGL	Tag7-like family protein	GB:AC011492 Direct submitted (07-OCT-1999) by Production Sequencing Facility, DOE Joint Genome Institute, 2800 Mitchell Drive, Walnut Creek, CA 94598, USA.	Mouse TAGL-alpha protein, gi: 10946624. Submitted (11-MAY-1999) Laboratory of Cancer Molecular Genetics, Institute of Gene Biology, Russian Academy of Sciences, 34/5 Vavilov Street, Moscow 117334, Russia	Secreted
sbg248602-CHP	Zinc Carboxy-peptidase	GB:AL035460 Direct submitted (20-MAR-2000) by Sanger Centre, Hinxton, Cambridgeshire, CB10 1SA, UK	Mouse metallocarboxy-peptidase CPX-1, AAD15985. Lei,Y., Xin,X., Morgan,D., Pintar,J.E. and Fricker,L.D, 1999, DNA Cell Biol. 18:175-185.	Secreted
sbg219473-HNKS	HNK-sulfotrans-ferase	GB:AP001087 Direct submitted (25-JAN-2000) by the Institute of Physical and Chemical Research (RIKEN), Genomic Sciences Center (GSC); Kitasato Univ., 1-15-1 Kitasato, Sagamihara, Kanagawa 228-8555, Japan.	Human GalNAc 4-sulfo-transferase, gi:11990885. Habuchi,O. and Okuda,T. J. Biol. Chem. 275 (51), 40605-40613 (2000)	Membrane-bound

Table III.

Gene Name	Uses	Associated Diseases
sbg123493-SLITa	An embodiment of the invention may be the use of sbg123493-SLITa, a secreted protein, to bind Robo receptors and have an evolutionarily conserved role in repulsive axon guidance and may be useful for the prevention and treatment of diseases in spinal cord, thyroid gland, ovary, prostate, renal gland, small intestine, heart, trachea, thymus, lymph node, muscular system and colon. sbg123493-SLITa may also be used in the treatment of pineal tumors and alleviation of precocious puberty. Close homologs of sbg123493-SLITa are rat protein-Slit protein and pineal gland specific gene-1 protein.	Diseases in spinal cord, thyroid gland, ovary, prostate, renal gland, small intestine, heart, trachea, thymus, lymph node, muscular system and colon, pineal tumors and alleviation of precocious puberty
sbg14936-EGFa	An embodiment of the invention is the use of sbg14936-EGFa, a secreted protein, to treat colorectal carcinomas, and peptic ulcer healing. The closest homologue to sbg14936-EGFa is high-molecular-weight *proteins with multiple EGF-like motifs.* Polypeptides with EGF-like and/or cadherin-like repeats have been used to stimulate the growth of various epidermal and epithelial tissues *in vivo* and *in vitro* and of some fibroblasts in cell culture.	Neurodegenerative disorders, trauma, natural blinding, colorectal carcinomas and peptic ulcer healing
SBh80018-.cyastin-related	An embodiment of the invention is the use of SBh80018-cyastin-related to treat or prevent tissue damage associated with brain hemorrhage.	Autoimmune disorder, hematopoietic disorder, wound healing disorder, viral and bacterial infection, cancer, neurological disorder, brain haemorrhage, tissue damage, inflammation, and protection and remodeling of the eye
SBh74552-trypsinogen	An embodiment of the invention is the use of SBh74552-trypsinogen to treat clot formation induced by myocardial infarction and reocclusion following angioplasty or pulmonary thromboembolism. Close homologues to of SBh74552-trypsinogen are used to treat clot formation and for treating associated gastrointestinal and haematopoietic disorders.	Autoimmune disorder, hematopoietic disorder, wound healing disorder, viral and bacterial infection, cancer, clot formation in myocardial infarction, reocclusion following angioplasty or pulmonary thromboembolism, gastrointestinal disorders

Table III (cont).

Gene Name	Uses	Associated Diseases
sbg90060-IGFBP	An embodiment of the invention is the use of sbg90060-IGFBP, in the treatment of a wide range of disease states including cancer, diabetes, vascular disease, asthma, and growth disorders. Close homologs of sbg90060-IGFBP are Insulin-like growth factor (IGF) binding proteins (IGFBP). IGFBP when occupied by IGF, combines with an acid-labile glycoprotein subunit (ALS) to form a high molecular weight complex. The IGFBPs regulate somatic growth and cellular proliferation both in vivo and in vitro. The IGFBPs also appear to have emerging roles in the mechanisms underlying human cancer. Future research on its physiology may have advancements in the treatment of a wide range of disease states including cancer, diabetes, vascular disease, asthma, and growth disorders (Wetterau LA, Moore MG, Lee KW, Shim ML, Cohen P, 1999, Mol Genet Metab 68:161-81).	Cancer, infection, autoimmune disorder, hematopoietic disorder, wound healing disorder, inflammation, diabetes, vascular disease, asthma, and growth isorders
sbg97078-ANGIOa	An embodiment of the invention is the use of sbg97078-ANGIOa, in treating hypertension, heart disease, and kidney disease, related to unbalanced levels of angiotensin II/vasopressin receptors. A close homolog of sbg97078-ANGIOa is angiotensin II/vasopressin receptors. Angiotensin II/vasopressin receptors couple to adenylate cyclase and responds with equal sensitivity to Ang II and AVP. Ang II receptors respond to the neurotransmitter angiotensin II whilst AVP receptors respond to arginine vasopressin. Vasopressin receptor mediates many central and peripheral actions of vasopressin, including intracellular calcium mobilization. Thus the proteins, antibodies, agonists and antagonists can be used for treating, e.g. hypertension, heart disease, and kidney disease, related to unbalanced levels of angiotensin II/vasopressin receptor (Howl J, Wheatley M, 1995 Gen Pharmacol 26:1143-52; Grazzini E, Boccara G, Joubert D, Trueba M, Durroux T, Guillon G, Gallo-Payet N, Chouinard L, Payet MD, Serradeil Le Gal C, 1998 Adv Exp Med Biol 449:325-34).	Cancer, infection, autoimmune disorder, hematopoietic disorder, wound healing disorder, inflammation hypertension, heart disease, and kidney disease
sbg68091-CMP	An embodiment of the invention is the use of sbg68091-CMP, in repairing damaged cartilage in joints, such as in osteoarthritis and rheumatoid arthritis. A close homolog of sbg68091-CMP is Matrilin-1. The matrilin family shares a common structure made up of von Willebrand factor A domains, epidermal growth factor-like domains and a coiled coil alpha-helical module (Deak F, Wagener R, Kiss I, Paulsson M, 1999. Matrix Biol 18:55-64). Matrilin-1, cartilage matrix protein (CMP), is a major component of the extracellular matrix of nonarticular cartilage, and it binds to collagen.	Cancer, infection, autoimmune disorder, hematopoietic disorder, wound healing disorder, inflammation rheumatoid arthritis, and osteoarthritis.

Table III (cont).

Gene Name	Uses	Associated Diseases
sbg18525-LRR	An embodiment of the invention is the use of sbg18525-LRR a member of the leucine-rich repeat protein family, in immunization , protein-protein interactions, such as cell adhesion or receptor-ligand binding and neuronal LRR may be an important component of the pathophysiological response to brain injury. Close homologs of sbg18525-LRR are leucine-rich repeat (LRR) proteins such as connectin, slit, chaoptin, and toll. These proteins have important roles in neuronal development and the adult nervous system as cell adhesion molecules (Taguchi A, Wanaka A, Mori T, Matsumoto K, Imai Y, Tagaki T, Tohyama M, 1996, Brain Res Mol Brain Res;35:31-4). At least one LRR was shown to be specifically expressed on B cells, suggesting its role in immunization (Miyake K, Yamashita Y, Ogata M, Sudo T, Kimoto M, 1995. J Immunol 154:3333-40). Some studies have shown that brain injury can cause over expression of neuronal LRR, suggesting that neuronal LRR may be an important component of the pathophysiological response to brain injury (Ishii N, Wanaka A, Tohyama M, 1996, Brain Res Mol Brain Res 40: 148-52)..	Cancer, infection, autoimmune disorder, hematopoietic disorder, wound healing disorder, inflammation, gastrointestinal ulceration, and diseases in spinal cord, thyroid gland, heart, trachea, thymus, lymph node, muscular system, and nervous system
SBh45597-trypsin inhibitor	An embodiment of the invention is the use of SBh45597-trypsin inhibitor in vesicle targeting. The Rabs are a subfamily within the large group of small GTP-binding proteins and have been showed to play a role in vesicle targeting. Like RAS, they cycle between active GTP-bound and inactive GDP-bound forms with both transitions to require additional factors: GTPase-activating proteins (GAPs) and guanine nucleotide exchange factors (GEFs). The GDP-bound form is also a target for a GDI (GDP dissociation inhibitor), a slightly-misnamed but remarkable protein which extracts the GDP-Rab (including its very hydrophobic isoprenoid groups) from the membrane, allowing it to return via the cytosol to its membrane of origin. (Armstrong J. Int J Biochem Cell Biol 2000 Mar;32(3):303-7).	Acute respiratory disease, AIDs, allergy, atherosclerosis, cancer, biabetes, cerebral neoplasm, immune disorder, imflasmmatory disorder, rheumatoid arthritis, viral infection.
sbg34640-CALa	An embodiment of the invention is the use of sbg34640-CALa, a secreted protein, in the diagnosis and treatment of cancer. Close homologues to sbg34640-CALa are S100 calcium-binding protein A11 (calgizzarin) and other EF-hand calcium binding proteins and more specifically to s-100/CABP like proteins. S100 calcium-binding protein A11 (calgizzarin) binds two calcium ions per molecule with an affinity similar to that of the s-100 proteins. s-100/CABP like proteins are useful in diagnosis and treatment of cancer. (Fan, Y., Leung, D., Houck, K.A., Yan, S., Kao, J. Calgizzarin (endothelial monocyte-activating polypeptide ((EMAP) Submitted JAN-1996 to the EMBL/GenBank/DDBJ databases. ACCESSION NO: P50543.).	Infections, cancers, autoimmune disorders, wound healing disorder and hematopoietic disorder

Table III (cont).

Gene Name	Uses	Associated Diseases
sbg14849LO	An embodiment of the invention is the use of sbg14849LO in the biogenesis of connective tissue matrices by crosslinking the extracellular matrix proteins, collagen and elastin or in the treatment of osteoporotic bone. A close homologue of sbg14849LO is lysyl oxidase (LO). LO is a cuproenzyme that plays a critical role in the biogenesis of connective tissue matrices by crosslinking the extracellular matrix proteins, collagen and elastin. Levels of LO increase in many fibrotic diseases, while expression of the enzyme is decreased in some diseases related to impaired copper metabolism. Transforming growth factor-beta, platelet-derived growth factor, angiotensin II, retinoic acid, fibroblast growth factor, and altered serum conditions can affect LO expression. It has also become increasingly evident that LO may have other important biological functions (Smith-Mungo LI, and Kagan HM, 1998, Matrix Biol 16:387-98). In mineralizing tissues, a relatively low level of lysyl hydroxylation results in low levels of hydroxylysyl pyridinoline, and the occurrence of the largely bone specific lysyl pyridinoline and pyrrolic cross-links (Knott L, and Bailey AJ, 1998, Bone 22:181-7).	Cancer, infection, autoimmune disorder, hematopoietic disorder, wound healing disorder, inflammation, fibrotic diseases, and metabolic bone diseases
SBh35812-CALGIZ-ZARIN	An embodiment of the invention is the use of SBh35812-CALGIZ-ZARIN to activate host response mechanisms. Close homologues of SBh35812-CALGIZ-ZARIN are cytokines and S-100 PROTEINS.	Autoimmune disorder, hematopoietic disorder, wound healing disorder, viral and bacterial infection, cancer, melanoma cance, cerebral dysfunction
sbg37967-ECMPa	An embodiment of the invention is the use of sbg37967-ECMPa, a secreted protein, in wound healing and treatment of inflammatory diseases. A close homologue to sbg37967-ECMPa is extracellular matrix protein 2 (pECM2). pECM2 expressed predominantly in adipose and female-specific tissues and its chromosomal localization to 9q22.3 and participates in protein-protein interactions and/or cell-ECM recognition processes (Nishiu,J., Tanaka,T. and Nakamura,Y. 1998. Genomics 52, 378-381).	Cancer, autoimmune disease, inflammatory diseases, wound healing and hematopoietic disorder
sbg15037-SER	An embodiment of the invention is the use of sbg15037-SER in the diagnosis of testicular tumors. sbg15037-SER is a membrane-type serine protease which shows a trypsin-like cleavage activity. A close homologue to sbg15037-SER is testisin, a new human serine proteinase, which is abundantly expressed only in the testis and is lost in testicular tumors. These findings about testisin demonstrate a new cell surface serine proteinase, loss of which may have a role in the progression of testicular tumors of germ cell origin. (Hooper JD, Nicol DL, Dickinson JL, Eyre HJ, Scarman AL, Normyle JF, Stuttgen MA, Douglas ML, Loveland KA, Sutherland GR, and Antalis TM, 1999, Cancer Res 59:3199-205).	Cancer, including testicular turmors, infection, autoimmune disorder, hematopoietic disorder, wound healing disorders, and inflammation

Table III (cont).

Gene Name	Uses	Associated Diseases
sbg23161-EGFa	An embodiment of the invention is the use of sbg23161-EGFa, a secreted protein, in regulating vascular smooth muscle cell proliferation, e.g. for enhancing neurological functions or treating neoplasia and other disorders. A close homologue to sbg23161-EGFa is human extracellular/epidermal growth factor-like protein(EEGF). This EEGF protein is useful for regulating vascular smooth muscle cell proliferation, e.g. for enhancing neurological functions or treating neoplasia and other disorders (LI HS and OLSEN H, New isolated extracellular/epidermal growth factor, Accession Number W79739, HUMAN GENOME SCI INC).	Cancer, autoimmune disorders, wound healing disorders, infections, and hemotopoietic disorders
sbg82008-TGFa,b	An embodiment of the invention is the use of sbg82008-TGFa,b in growth control and hence the etiology of cancer, cell differentiation and development. sbg82008-TGFa,b contains the Prosite consensus pattern (PDOC00223) for TGF beta family members. Close homologues of sbg82008-TGFa,b are TGF-beta proteins. TGF-beta proteins are known to be involved in growth control and hence the etiology of cancer (*Anticancer Res* 1999 Nov-Dec;19(6A):4791-807), cell differentiation and development. A TGF-beta signaling pathway constitutes a tumor suppressor path (*Cytokine Growth Factor Rev* 2000 Apr 1;11(1-2):159-168).	Cancer (eg., lymphoma, leukemia, renal cell carcinoma, melanoma, lung cancer), infection (viral disease, (eg hepatitis A and C), parasitic disease, bacterial disease), inflammation, autoimmune disorder (eg multiple sclerosis, Type I diabetes), infertility, miscarriage, hematopoietic disorder, wound healing disorder, inflammatory diseases, inflammatory bowel disease, cystic fibrosis, immune deficiency, thrombocytopenia, chronic obstructive pulmonary disease
sbg27142-IGBb	An embodiment of the invention is the use of sbg27142-IGBb in the diagnosis and/or treatment of cancer and autoimmune disorders of the nervous system. A close homologue to sbg27142-IGBb is the mouse cell adhesion molecule (gi:11862939) that has been associated with transformation of osteoblasts and the mouse gene Punc that is expressed predominantly in the developing nervous system (Salbaum, J.M. 1998 Mech. Dev. 71 (1-2), 201-204).	Cancer, infection diseases, autoimmune disorder, wound healing disorder and hematopoietic disorder
sbg239881-TAGL	An embodiment of the invention is the use of sbg239881-TAGL to inhibit tumor growth and induce apoptosis and/or may also be useful as probes for gene mapping and detection of tag7 gene expression. Close homologues to sbg239881-TAGL and its promoter region are genes of the tumor necrosis factor (TNF). The tag7 coding sequences are also useful as probes for gene mapping and detection of tag7 gene expression (Kiselev SL, Kustikova OS, Korobko EV, Prokhortchouk EB, Kabishev AA, Lukanidin EM, Georgiev GP, 1998, J Biol Chem 273:18633-9).	Cancer, infection, autoimmune disorder, hematopoietic disorder, wound healing disorders

Table III (cont).

Gene Name	Uses	Associated Diseases
sbg248602-CHP	Due to the carboxypeptidase activity required for processing of various neuropeptides and hormones, an embodiment of the invention is the use of sbg248602-CHP in treatments of neurodegenerative disorders and developmental abnormalities. Close homologues to sbg248602-CHP are peptidases that catalyze the removal of c-terminal basic amino acid residues, and is involved in processing of neuropeptides and hormones in secretory vesicles (Manser E, Fernandez D, Loo L, Goh PY, Monfries C, Hall C, and Lim L, 1990, Biochem J 267:517-25). Some enzymes from this family have been isolated in multiple forms from both soluble and membrane-bound compartments, and are demonstrated to co-secrete with peptides from pancreatic and adrenal cells. Single mRNA species have been shown to yield multiple forms of similar peptidases (Manser E, Fernandez D, and Lim L, 1991, Biochem J 280:695-701).	Cancer, infection, autoimmune disorder, hematopoietic disorder, wound healing disorders, inflammation, neurodegenerative disorders, and developmental abnormalities
sbg219473-HNKS	An embodiment of the invention may be the use of sbg219473-HNKS in the development of the nervous system, and may also be involved in the preferential reinervation of muscle nerves by motor axons after lesion. Close homologues to sbg219473-HNKS are sulfotransferases. Sulfotransferase is considered to be the key enzyme in the biosynthesis of the HNK-1 carbohydrate epitope, which is expressed on several neural adhesion glycoproteins and as a glycolipid, and is involved in cell interactions (Bakker,H., Friedmann,I., Oka,S., Kawasaki,T., Nifant'ev,N., Schachner,M., and Mantei,N., 1997, J. Biol. Chem. 272:29942-29946). The HNK-1 epitope is spatially and temporally regulated during the development of the nervous system. The biological function of the HNK-1 sulfotransferase may be related to the development of the nervous system, and also may be involved in the preferential reinervation of muscle nerves by motor axons after lesion (Jungalwala FB, 1994, Neurochem Res 19:945-57).	Cancer, infection, autoimmune disorder, hematopoietic disorder, wound healing disorders, inflammation, and peripheral neuropathies

Table IV. Quantitative, Tissue-specific mRNA expression detected using SybrMan

Quantitative, tissue-specific, mRNA expression patterns of the genes were measured using SYBR-Green Quantitative PCR (Applied Biosystems, Foster City, CA; see Schmittgen T.D. et al., Analytical Biochemistry 285:194-204, 2000) and human cDNAs prepared from various human tissues. Gene-specific PCR primers were designed using the first nucleic acid sequence listed in the Sequence List for each gene. Results are presented as the number of copies of each specific gene's mRNA detected in 1ng mRNA pool from each tissue. Two replicate mRNA measurements were made from each tissue RNA.

Table IV Cont

Gene Name	Tissue-Specific mRNA Expression (copies per ng mRNA; avg. ± range for 2 data points per tissue)									
	Brain	Heart	Lung	Liver	Kid-ney	Skele-tal muscle	Intes-tine	Spleen /lymph	Pla-centa	Testis
sbg123493-SLITa	9±3	70±31	13±3	-1±1	41±16	132 ±21	6±2	5±10	9±4	959 ±80
sbg14936-EGFa	516±3 4	2424± 72	550 ±56	129±7	1825 ±6	1503 ±168	218 ±26	423±4	629 ±39	1765 ±40
SBh80018-.cyastin-related	1±0	2±1	0±0	-7±4	2±3	6±4	-3±3	2±0	0±1	5258 ±259
SBh74552-.trypsinogen	-1±1	7±1	9±1	-10±1	1±3	4±1	3±0	10±3	5±0	5159 ±907
sbg90060-IGFBP	366 ±17	659 ±36	784 ±64	53±7	1035 ±189	119 ±15	109±4	531 ±12	582±8	207 ±13
sbg97078-ANGIOa	15±1	16±7	58±3	-6±1	18±1	4±1	37±2	91±5	244±3	688 ±18
sbg68091-CMP	1360 ±30	3596 ±59	1846 ±271	248 ±18	2596 ±146	2351 ±5	1646 ±112	486±4	3228 ±327	3204 ±42
sbg18525-LRR	4290± 157	367±6	47±4	7±0	263 ±10	69±7	401 ±62	39±3	119 ±17	307±1
SBh45597-.trypsin inhibitor	59±12	58±7	44±1	22±1	106 ±21	45±6	36±6	49±16	57±9	219 ±55
sbg34640-CALa	3006± 11	30001 ±197	98054 ±1290	4166± 228	39196 ±1674	9611 ±323	31417 ±619	70617 ±2786	203542 ±4017	20011 ±2747
sbg14849-LO	508 ±23	862 ±13	631±8	51±5	251 ±24	125 ±12	348 ±38	662 ±17	1404 ±138	721 ±69
SBh35812.-CALGIZ-ZARIN	345±1	20±1	11±1	-3±7	45±1	8±7	5±2	15±4	20±5	136 ±20
sbg37967-ECMPa	72±5	26±10	24±8	3±9	45±0	18±1	4±3	34±10	593 ±62	57±5
sbg15037-SER	291±9	256 ±24	284 ±18	302±7	312±6	298±8	264 ±17	256 ±4	277 ±14	316 ±55
sbg23161-EGFa	150±1	142±9	2063 ±68	348 ±20	1184± 80	79±13	809 ±41	1276 ±17	831 ±22	2635± 156

Table IV Cont

Gene Name	Tissue-Specific mRNA Expression (copies per ng mRNA; avg. ± range for 2 data points per tissue)									
	Brain	Heart	Lung	Liver	Kidney	Skeletal muscle	Intestine	Spleen /lymph	Placenta	Testis
sbg82008-TGFa,b	1542 ±96	651 ±49	858 ±37	555 ±30	818 ±248	829 ±47	321 ±28	721 ±108	1037 ±51	670 ±110
sbg2714-2IGBb	526±37	505±8	115±5	-6±9	91±3	3783±80	173±1	211±37	5218±240	354±39
sbg23988-1TAGL	3±1	2±0	6±1	2816 ±28	6±1	0±0	3±1	-2±5	4±0	780 ±20
sbg248602-CHP	134 ±10	989 ±16	539±3	3±5	1335 ±16	80±17	385 ±18	730 ±43	15644 ±309	921±9
sbg219473-HNKS	175 ±32	1075 ±81	2522 ±91	473 ±35	453 ±57	74±18	98±1	1121 ±12	10±6	2813 ±148

Table V. Additional diseases based on mRNA expression in specific tissues

Tissue Expression	Additional Diseases
Brain	Neurological and psychiatric diseases, including Alzheimers, parasupranuclear palsey, Huntington's disease, myotonic dystrophy, anorexia, depression, schizophrenia, headache, amnesias, anxiety disorders, sleep disorders, multiple sclerosis
Heart	Cardiovascular diseases, including congestive heart failure, dilated cardiomyopathy, cardiac arrhythmias, Hodgson's Disease, myocardial infarction, cardiac arrhythmias
Lung	Respiratory diseases, including asthma, Chronic Obstructive Pulmonary Disease, cystic fibrosis, acute bronchitis, adult respiratory distress syndrome
Liver	Dyslipidemia, hypercholesterolemia, hypertriglyceridemia, cirrhosis, hepatic encephalopathy, fatty hepatocirrhosis, viral and nonviral hepatitis, Type II Diabetes Mellitis, impaired glucose tolerance
Kidney	Renal diseases, including acute and chronic renal failure, acute tubular necrosis, cystinuria, Fanconi's Syndrome, glomerulonephritis, renal cell carcinoma, renovascular hypertension
Skeletal muscle	Eulenburg's Disease, hypoglycemia, obesity, tendinitis, periodic paralyses, malignant hyperthermia, paramyotonia congenita, myotonia congenita
Intestine	Gastrointestinal diseases, including Myotonia congenita, Ileus, Intestinal Obstruction, Tropical Sprue, Pseudomembranous Enterocolitis
Spleen/lymph	Lymphangiectasia, hypersplenism, angiomas, ankylosing spondylitis, Hodgkin's Disease, macroglobulinemia, malignant lymphomas, rheumatoid arthritis
Placenta	Choriocarcinoma, hydatidiform mole, placenta previa
Testis	Testicular cancer, male reproductive diseases, including low testosterone and male infertility
Pancreas	Diabetic ketoacidosis, Type 1 & 2 diabetes, obesity, impaired glucose tolerance

What is claimed is:

1. An isolated polypeptide selected from the group consisting of:
(a) an isolated polypeptide encoded by a polynucleotide comprising a sequence set forth in Table I;
(b) an isolated polypeptide comprising a polypeptide sequence set forth in Table I; and
(c) a polypeptide sequence of a gene set forth in Table I.

2. An isolated polynucleotide selected from the group consisting of:
(a) an isolated polynucleotide comprising a polynucleotide sequence set forth in Table I;
(b) an isolated polynucleotide of a gene set forth in Table I;
(c) an isolated polynucleotide comprising a polynucleotide sequence encoding a polypeptide set forth in Table I;
(d) an isolated polynucleotide encoding a polypeptide set forth in Table I;
(e) a polynucleotide which is an RNA equivalent of the polynucleotide of (a) to (d);
or a polynucleotide sequence complementary to said isolated polynucleotide.

3. An expression vector comprising a polynucleotide capable of producing a polypeptide of claim 1 when said expression vector is present in a compatible host cell.

4. A process for producing a recombinant host cell which comprises the step of introducing an expression vector comprising a polynucleotide capable of producing a polypeptide of claim 1 into a cell such that the host cell, under appropriate culture conditions, produces said polypeptide.

5. A recombinant host cell produced by the process of claim 4.

6. A membrane of a recombinant host cell of claim 5 expressing said polypeptide.

7. A process for producing a polypeptide which comprises culturing a host cell of claim 5 under conditions sufficient for the production of said polypeptide and recovering said polypeptide from the culture.

SEQUENCE LISTING

<110> SMITHKLINE BEECHAM CORPORATION
SMITHKLINE BEECHAM p.l.c.

<120> NOVEL COMPOUNDS

<130> GP50018

<140> TO BE ASSIGNED
<141> 2001-03-22

<150> 60/192,158
<151> 2000-03-24

<150> 60/192,668
<151> 2000-03-27

<150> 60/200,166
<151> 2000-04-27

<160> 66

<170> FastSEQ for Windows Version 3.0

<210> 1
<211> 771
<212> DNA
<213> Homo sapiens

<400> 1
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gaagtggctc cagaaaaggt gaactcaaaa gatggtcaga atgggagaaa aagttgggtg    720
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<210> 2
<211> 2694
<212> DNA
<213> Homo sapiens

<400> 2
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<210> 3
<211> 2982
<212> DNA
<213> Homo sapiens

<400> 3

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<211> 417
<212> DNA
<213> Homo sapiens

<400> 4
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<210> 5
<211> 726
<212> DNA
<213> Homo sapiens

<400> 5
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gattacacag tcagctccac tccccсttac ttggtctatt tgaaatctga ctacttgccc 120

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gacatcatgc taatcaagct gaaaacagag gctgaactca atgactatgt gaaattagcc     360
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aactga                                                                726
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<210> 6
<211> 732
<212> DNA
<213> Homo sapiens

<400> 6

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ttgccctgcg ctggagtcct gatccacccg ctttgggtga tcacagctgc acactgcaat     180
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<210> 7
<211> 1452
<212> DNA
<213> Homo sapiens

<400> 7

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gggggcccct ga 1452

<210> 8
<211> 1818
<212> DNA
<213> Homo sapiens

<400> 8
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<210> 9
<211> 3150
<212> DNA
<213> Homo sapiens

<400> 9
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<211> 3189
<212> DNA
<213> Homo sapiens

<400> 10

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<210> 11
<211> 1062
<212> DNA
<213> Homo sapiens

<400> 11

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<211> 1347
<212> DNA
<213> Homo sapiens

<400> 12

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<210> 13
<211> 1482
<212> DNA
<213> Homo sapiens

<400> 13

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<210> 14
<211> 1647
<212> DNA
<213> Homo sapiens

<400> 14
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<211> 861
<212> DNA
<213> Homo sapiens

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<210> 16
<211> 519
<212> DNA
<213> Homo sapiens

<400> 16

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<210> 17
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<212> DNA
<213> Homo sapiens

<400> 17

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<210> 18
<211> 2262
<212> DNA
<213> Homo sapiens

<400> 18

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Ile Thr Ser Leu Pro Ala Met His Leu Gly Leu Leu Ser Asp Leu Val
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Phe Ile Gly Val Phe Lys Leu Ile Tyr Leu Asp Leu Ser Ser Asn Asn
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Glu Thr Leu Phe Leu Ser Gly Asn Pro Trp Lys Cys Asn Cys Ser Phe
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Glu Gly Leu Ile Gly Cys Gly Glu Glu Asp Val Ile Glu Val Ala Pro
    210   215   220
Glu Lys Val Asn Ser Lys Asp Gly Gln Asn Gly Arg Lys Ser Trp Val
225   230   235   240
Lys Leu Ile Glu Cys Ile Leu Ile Thr Leu Gln Gly Pro Pro Leu Gly
                245   250   255

<210> 35
<211> 897
<212> PRT
<213> Homo sapiens

<400> 35
Met Gly Ser Gly Arg Val Pro Gly Leu Cys Leu Leu Val Leu Leu Val
1   5   10   15
His Ala Arg Ala Ala Gln Tyr Ser Lys Ala Ala Gln Asp Val Asp Glu
            20   25   30
Cys Val Glu Gly Thr Asp Asn Cys His Ile Asp Ala Ile Cys Gln Asn
        35   40   45
Thr Pro Arg Ser Tyr Lys Cys Ile Cys Lys Ser Gly Tyr Thr Gly Asp
    50   55   60
Gly Lys His Cys Lys Asp Val Asp Glu Cys Glu Arg Glu Asp Asn Ala
65   70   75   80
Gly Cys Val His Asp Cys Val Asn Ile Pro Gly Asn Tyr Arg Cys Thr

85 90 95
Cys Tyr Asp Gly Phe His Leu Ala His Asp Gly His Asn Cys Leu Asp
100 105 110
Val Asp Glu Cys Ala Glu Gly Asn Gly Gly Cys Gln Gln Ser Cys Val
115 120 125
Asn Met Met Gly Ser Tyr Glu Cys His Cys Arg Glu Gly Phe Phe Leu
130 135 140
Ser Asp Asn Gln His Thr Cys Ile Gln Arg Pro Glu Glu Gly Met Asn
145 150 155 160
Cys Met Asn Lys Asn His Gly Cys Ala His Ile Cys Arg Glu Thr Pro
165 170 175
Lys Gly Gly Ile Ala Cys Glu Cys Arg Pro Gly Phe Glu Leu Thr Lys
180 185 190
Asn Gln Arg Asp Cys Lys Cys Glu Ile Ile Gly Met Ala Val Thr Cys
195 200 205
Asn Tyr Gly Asn Gly Gly Cys Gln His Thr Cys Asp Asp Thr Glu Gln
210 215 220
Gly Pro Arg Cys Gly Cys His Ile Lys Phe Val Leu His Thr Asp Gly
225 230 235 240
Lys Thr Cys Ile Glu Thr Cys Ala Val Asn Asn Gly Gly Cys Asp Ser
245 250 255
Lys Cys His Asp Ala Ala Thr Gly Val His Cys Thr Cys Pro Val Gly
260 265 270
Phe Met Leu Gln Pro Asp Arg Lys Thr Cys Lys Asp Ile Asp Glu Cys
275 280 285
Arg Leu Asn Asn Gly Gly Cys Asp His Ile Cys Arg Asn Thr Val Gly
290 295 300
Ser Phe Glu Cys Ser Cys Lys Lys Gly Tyr Lys Leu Leu Ile Asn Glu
305 310 315 320
Arg Asn Cys Gln Asp Ile Asp Glu Cys Ser Phe Asp Arg Thr Cys Asp
325 330 335
His Ile Cys Val Asn Thr Pro Gly Ser Phe Gln Cys Leu Cys His Arg
340 345 350
Gly Tyr Leu Leu Tyr Gly Ile Thr His Cys Gly Asp Val Asp Glu Cys
355 360 365
Ser Ile Asn Arg Gly Gly Cys Arg Phe Gly Cys Ile Asn Thr Pro Gly
370 375 380
Ser Tyr Gln Cys Thr Cys Pro Ala Gly Gln Gly Arg Leu His Trp Asn
385 390 395 400
Gly Lys Asp Cys Thr Glu Pro Leu Lys Cys Gln Gly Ser Pro Gly Ala
405 410 415
Ser Lys Ala Met Leu Ser Cys Asn Arg Ser Gly Lys Lys Asp Thr Cys
420 425 430
Ala Leu Thr Cys Pro Ser Arg Ala Arg Phe Leu Pro Glu Ser Glu Asn
435 440 445
Gly Phe Thr Val Ser Cys Gly Thr Pro Ser Pro Arg Ala Ala Pro Ala
450 455 460
Arg Ala Gly His Asn Gly Asn Ser Thr Asn Ser Asn His Cys His Glu
465 470 475 480
Ala Ala Val Leu Ser Ile Lys Gln Arg Ala Ser Phe Lys Ile Lys Asp
485 490 495
Ala Lys Cys Arg Leu His Leu Arg Asn Lys Gly Lys Thr Glu Glu Ala
500 505 510
Gly Arg Ile Thr Gly Pro Gly Gly Ala Pro Cys Ser Glu Cys Gln Val
515 520 525
Thr Phe Ile His Leu Lys Cys Asp Ser Ser Arg Lys Gly Lys Gly Arg
530 535 540
Arg Ala Arg Thr Pro Pro Gly Lys Glu Val Thr Arg Leu Thr Leu Glu
545 550 555 560

Leu Glu Ala Glu Gln Leu Phe Leu Leu Pro Asp Thr His Gly His Pro
565 570 575
Pro Pro Ala Ser Cys Gly Leu Pro Cys Leu Arg Gln Arg Met Glu Arg
580 585 590
Arg Leu Lys Gly Ser Leu Lys Met Leu Arg Lys Ser Ile Asn Gln Asp
595 600 605
Arg Phe Leu Leu Arg Leu Ala Gly Leu Asp Tyr Glu Leu Ala His Lys
610 615 620
Pro Gly Leu Val Ala Gly Glu Arg Ala Glu Pro Met Glu Ser Cys Arg
625 630 635 640
Pro Gly Gln His Arg Ala Gly Thr Lys Cys Val Gln Cys Ser Pro Gly
645 650 655
His Tyr Tyr Asn Thr Ser Ile His Arg Cys Ile Arg Cys Ala Met Gly
660 665 670
Ser Tyr Gln Pro Asp Phe Arg Gln Asn Phe Cys Ser Arg Cys Pro Gly
675 680 685
Asn Thr Ser Thr Asp Phe Asp Gly Ser Thr Ser Val Ala Gln Cys Lys
690 695 700
Asn Arg Gln Cys Gly Gly Glu Leu Gly Glu Phe Thr Gly Tyr Ile Glu
705 710 715 720
Ser Pro Asn Tyr Pro Gly Asn Tyr Pro Ala Gly Val Glu Cys Ile Trp
725 730 735
Asn Ile Asn Pro Pro Pro Lys Arg Lys Ile Leu Ile Val Val Pro Glu
740 745 750
Ile Phe Leu Pro Ser Glu Asp Glu Cys Gly Asp Val Leu Val Met Arg
755 760 765
Lys Asn Ser Ser Pro Ser Ser Ile Thr Thr Tyr Glu Thr Cys Gln Thr
770 775 780
Tyr Glu Arg Pro Ile Ala Phe Thr Ala Arg Ser Arg Lys Leu Trp Ile
785 790 795 800
Asn Phe Lys Thr Ser Glu Ala Asn Ser Ala Arg Gly Phe Gln Ile Pro
805 810 815
Tyr Val Thr Tyr Asp Glu Asp Tyr Glu Gln Leu Val Glu Asp Ile Val
820 825 830
Arg Asp Gly Arg Leu Tyr Ala Ser Glu Asn His Gln Glu Ile Leu Lys
835 840 845
Asp Lys Lys Leu Ile Lys Ala Phe Phe Glu Val Leu Ala His Pro Gln
850 855 860
Asn Tyr Phe Lys Tyr Thr Glu Lys His Lys Glu Met Leu Pro Lys Ser
865 870 875 880
Phe Ile Lys Leu Leu Arg Ser Lys Val Ser Ser Phe Leu Arg Pro Tyr
885 890 895
Lys

<210> 36
<211> 993
<212> PRT
<213> Homo sapiens

<400> 36
Met Gly Ser Gly Arg Val Pro Gly Leu Cys Leu Leu Val Leu Leu Val
1 5 10 15
His Ala Arg Ala Ala Gln Tyr Ser Lys Ala Ala Gln Asp Val Asp Glu
20 25 30
Cys Val Glu Gly Thr Asp Asn Cys His Ile Asp Ala Ile Cys Gln Asn
35 40 45
Thr Pro Arg Ser Tyr Lys Cys Ile Cys Lys Ser Gly Tyr Thr Gly Asp
50 55 60

Gly Lys His Cys Lys Asp Val Asp Glu Cys Glu Arg Glu Asp Asn Ala
65 70 75 80
Gly Cys Val His Asp Cys Val Asn Ile Pro Gly Asn Tyr Arg Cys Thr
85 90 95
Cys Tyr Asp Gly Phe His Leu Ala His Asp Gly His Asn Cys Leu Asp
100 105 110
Val Asp Glu Cys Ala Glu Gly Asn Gly Gly Cys Gln Gln Ser Cys Val
115 120 125
Asn Met Met Gly Ser Tyr Glu Cys His Cys Arg Glu Gly Phe Phe Leu
130 135 140
Ser Asp Asn Gln His Thr Cys Ile Gln Arg Pro Glu Glu Gly Met Asn
145 150 155 160
Cys Met Asn Lys Asn His Gly Cys Ala His Ile Cys Arg Glu Thr Pro
165 170 175
Lys Gly Gly Ile Ala Cys Glu Cys Arg Pro Gly Phe Glu Leu Thr Lys
180 185 190
Asn Gln Arg Asp Cys Lys Leu Thr Cys Asn Tyr Gly Asn Gly Gly Cys
195 200 205
Gln His Thr Cys Asp Asp Thr Glu Gln Gly Pro Arg Cys Gly Cys His
210 215 220
Ile Lys Phe Val Leu His Thr Asp Gly Lys Thr Cys Ile Glu Thr Cys
225 230 235 240
Ala Val Asn Asn Gly Gly Cys Asp Ser Lys Cys His Asp Ala Ala Thr
245 250 255
Gly Val His Cys Thr Cys Pro Val Gly Phe Met Leu Gln Pro Asp Arg
260 265 270
Lys Thr Cys Lys Asp Ile Asp Glu Cys Arg Leu Asn Asn Gly Gly Cys
275 280 285
Asp His Ile Cys Arg Asn Thr Val Gly Ser Phe Glu Cys Ser Cys Lys
290 295 300
Lys Gly Tyr Lys Leu Leu Ile Asn Glu Arg Asn Cys Gln Asp Ile Asp
305 310 315 320
Glu Cys Ser Phe Asp Arg Thr Cys Asp His Ile Cys Val Asn Thr Pro
325 330 335
Gly Ser Phe Gln Cys Leu Cys His Arg Gly Tyr Leu Leu Tyr Gly Ile
340 345 350
Thr His Cys Gly Asp Val Asp Glu Cys Ser Ile Asn Arg Gly Gly Cys
355 360 365
Arg Phe Gly Cys Ile Asn Thr Pro Gly Ser Tyr Gln Cys Thr Cys Pro
370 375 380
Ala Gly Gln Gly Arg Leu His Trp Asn Gly Lys Asp Cys Thr Glu Pro
385 390 395 400
Leu Lys Cys Gln Gly Ser Pro Gly Ala Ser Lys Ala Met Leu Ser Cys
405 410 415
Asn Arg Ser Gly Lys Lys Asp Thr Cys Ala Leu Thr Cys Pro Ser Arg
420 425 430
Ala Arg Phe Leu Pro Glu Ser Glu Asn Gly Phe Thr Val Ser Cys Gly
435 440 445
Thr Pro Ser Pro Arg Ala Ala Pro Ala Arg Ala Gly His Asn Gly Asn
450 455 460
Ser Thr Asn Ser Asn His Cys His Glu Ala Ala Val Leu Ser Ile Lys
465 470 475 480
Gln Arg Ala Ser Phe Lys Ile Lys Asp Ala Lys Cys Arg Leu His Leu
485 490 495
Arg Asn Lys Gly Lys Thr Glu Glu Ala Gly Arg Ile Thr Gly Pro Gly
500 505 510
Gly Ala Pro Cys Ser Glu Cys Gln Val Thr Phe Ile His Leu Lys Cys
515 520 525
Asp Ser Ser Arg Lys Gly Lys Gly Arg Arg Ala Arg Thr Pro Pro Gly

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        530                 535                 540
    Lys Glu Val Thr Arg Leu Thr Leu Glu Leu Glu Ala Glu Val Arg Ala
    545                 550                 555                 560
    Glu Glu Thr Thr Ala Ser Cys Gly Leu Pro Cys Leu Arg Gln Arg Met
                    565                 570                 575
    Glu Arg Arg Leu Lys Gly Ser Leu Lys Met Leu Arg Lys Ser Ile Asn
                580                 585                 590
    Gln Asp Arg Phe Leu Leu Arg Leu Ala Gly Leu Asp Tyr Glu Leu Ala
            595                 600                 605
    His Lys Pro Gly Leu Val Ala Gly Glu Arg Ala Glu Pro Met Glu Ser
        610                 615                 620
    Cys Arg Pro Gly Gln His Arg Ala Gly Thr Lys Cys Val Ser Cys Pro
    625                 630                 635                 640
    Gln Gly Thr Tyr Tyr His Gly Gln Thr Glu Gln Cys Val Pro Cys Pro
                    645                 650                 655
    Ala Gly Thr Phe Gln Glu Arg Glu Gly Gln Leu Ser Cys Asp Leu Cys
                660                 665                 670
    Pro Gly Ser Asp Ala His Gly Pro Leu Gly Ala Thr Asn Val Thr Thr
            675                 680                 685
    Cys Ala Gly Gln Cys Pro Pro Gly Gln His Ser Val Asp Gly Phe Lys
        690                 695                 700
    Pro Cys Gln Pro Cys Pro Arg Gly Thr Tyr Gln Pro Glu Ala Gly Arg
    705                 710                 715                 720
    Thr Leu Cys Phe Pro Cys Gly Gly Gly Leu Thr Thr Lys His Glu Gly
                    725                 730                 735
    Ala Ile Ser Phe Gln Asp Cys Asp Thr Lys Val Gln Cys Ser Pro Gly
                740                 745                 750
    His Tyr Tyr Asn Thr Ser Ile His Arg Cys Ile Arg Cys Ala Met Gly
            755                 760                 765
    Ser Tyr Gln Pro Asp Phe Arg Gln Asn Phe Cys Ser Arg Cys Pro Gly
        770                 775                 780
    Asn Thr Ser Thr Asp Phe Asp Gly Ser Thr Ser Val Ala Gln Cys Lys
    785                 790                 795                 800
    Asn Arg Gln Cys Gly Gly Glu Leu Gly Glu Phe Thr Gly Tyr Ile Glu
                    805                 810                 815
    Ser Pro Asn Tyr Pro Gly Asn Tyr Pro Ala Gly Val Glu Cys Ile Trp
                820                 825                 830
    Asn Ile Asn Pro Pro Pro Lys Arg Lys Ile Leu Ile Val Val Pro Glu
            835                 840                 845
    Ile Phe Leu Pro Ser Glu Asp Glu Cys Gly Asp Val Leu Val Met Arg
        850                 855                 860
    Lys Asn Ser Ser Pro Ser Ser Ile Thr Thr Tyr Glu Thr Cys Gln Thr
    865                 870                 875                 880
    Tyr Glu Arg Pro Ile Ala Phe Thr Ala Arg Ser Arg Lys Leu Trp Ile
                    885                 890                 895
    Asn Phe Lys Thr Ser Glu Ala Asn Ser Ala Arg Gly Phe Gln Ile Pro
                900                 905                 910
    Tyr Val Thr Tyr Asp Glu Asp Tyr Glu Gln Leu Val Glu Asp Ile Val
            915                 920                 925
    Arg Asp Gly Arg Leu Tyr Ala Ser Glu Asn His Gln Glu Ile Leu Lys
        930                 935                 940
    Asp Lys Lys Leu Ile Lys Ala Phe Phe Glu Val Leu Ala His Pro Gln
    945                 950                 955                 960
    Asn Tyr Phe Lys Tyr Thr Glu Lys His Lys Glu Met Leu Pro Lys Ser
                    965                 970                 975
    Phe Ile Lys Leu Leu Arg Ser Lys Val Ser Ser Phe Leu Arg Pro Tyr
                980                 985                 990
    Lys
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<210> 37
<211> 138
<212> PRT
<213> Homo sapiens

<400> 37
Met Val Arg Leu Cys Gln Ala Leu Leu Leu Leu Val Ala Thr Val Ala
1 5 10 15
Leu Ala Ser Arg Arg Phe Gln Ala Trp Gly Ser Thr Lys Val Val Arg
20 25 30
Thr Phe Gln Asp Ile Pro Gln Asn Tyr Val Tyr Val Gln Gln Ala Leu
35 40 45
Trp Phe Ala Met Lys Glu Tyr Asn Lys Ala Ser Phe Ser Ile Thr Ser
50 55 60
Ser Ala Leu Gly Lys Glu Tyr Lys Leu Lys Val Thr Asp Ser Leu Glu
65 70 75 80
Tyr Tyr Ile Glu Val Lys Ile Ala Arg Thr Ile Cys Lys Lys Ile Ser
85 90 95
Glu Asp Glu Asn Cys Ala Phe Gln Glu Asp Pro Lys Met Gln Lys Val
100 105 110
Val Phe Cys Thr Phe Ile Val Ala Ser Lys Pro Trp Lys Phe Glu Leu
115 120 125
Thr Met Leu Lys Lys Gln Cys Lys Asp Met
130 135

<210> 38
<211> 241
<212> PRT
<213> Homo sapiens

<400> 38
Met Lys Phe Ile Leu Leu Trp Ala Leu Leu Asn Leu Thr Val Ala Leu
1 5 10 15
Ala Phe Asn Pro Asp Tyr Thr Val Ser Ser Thr Pro Pro Tyr Leu Val
20 25 30
Tyr Leu Lys Ser Asp Tyr Leu Pro Cys Ala Gly Val Leu Ile His Pro
35 40 45
Leu Trp Val Ile Thr Ala Ala His Cys Asn Leu Pro Lys Leu Arg Val
50 55 60
Ile Leu Gly Val Thr Ile Pro Ala Asp Ser Asn Glu Lys His Leu Gln
65 70 75 80
Val Ile Gly Tyr Glu Lys Met Ile His His Pro His Phe Ser Val Thr
85 90 95
Ser Ile Asp His Asp Ile Met Leu Ile Lys Leu Lys Thr Glu Ala Glu
100 105 110
Leu Asn Asp Tyr Val Lys Leu Ala Asn Leu Pro Tyr Gln Thr Ile Ser
115 120 125
Glu Asn Thr Met Cys Ser Val Ser Thr Trp Ser Tyr Asn Val Cys Asp
130 135 140
Ile Tyr Lys Glu Pro Asp Ser Leu Gln Thr Val Asn Ile Ser Val Ile
145 150 155 160
Ser Lys Pro Gln Cys Arg Asp Ala Tyr Lys Thr Tyr Asn Ile Thr Glu
165 170 175
Asn Met Leu Cys Val Gly Ile Val Pro Gly Arg Arg Gln Pro Cys Lys
180 185 190
Glu Val Ser Ala Ala Pro Ala Ile Cys Asn Gly Met Leu Gln Gly Ile
195 200 205
Leu Ser Phe Ala Asp Gly Cys Val Leu Arg Ala Asp Val Gly Ile Tyr

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    210                 215                 220
Ala Lys Ile Phe Tyr Tyr Ile Pro Trp Ile Glu Asn Val Ile Gln Asn
225                 230                 235                 240
Asn


      <210> 39
      <211> 243
      <212> PRT
      <213> Homo sapiens

      <400> 39
Met Thr Glu Lys Ser Trp Asn Phe Leu Ser Met Leu Leu Phe Pro Val
 1               5                  10                  15
Ala Leu Ala Phe Asn Pro Asp Tyr Thr Val Ser Ser Thr Pro Pro Tyr
            20                  25                  30
Leu Val Tyr Leu Lys Ser Asp Tyr Leu Pro Cys Ala Gly Val Leu Ile
        35                  40                  45
His Pro Leu Trp Val Ile Thr Ala Ala His Cys Asn Leu Pro Lys Leu
    50                  55                  60
Arg Val Ile Leu Gly Val Thr Ile Pro Ala Asp Ser Asn Glu Lys His
65                  70                  75                  80
Leu Gln Val Ile Gly Tyr Glu Lys Met Ile His His Pro His Phe Ser
                85                  90                  95
Val Thr Ser Ile Asp His Asp Ile Met Leu Ile Lys Leu Lys Thr Glu
            100                 105                 110
Ala Glu Leu Asn Asp Tyr Val Lys Leu Ala Asn Leu Pro Tyr Gln Thr
        115                 120                 125
Ile Ser Glu Asn Thr Met Cys Ser Val Ser Thr Trp Ser Tyr Asn Val
    130                 135                 140
Cys Asp Ile Tyr Lys Glu Pro Asp Ser Leu Gln Thr Val Asn Ile Ser
145                 150                 155                 160
Val Ile Ser Lys Pro Gln Cys Arg Asp Ala Tyr Lys Thr Tyr Asn Ile
                165                 170                 175
Thr Glu Asn Met Leu Cys Val Gly Ile Val Pro Gly Arg Arg Gln Pro
            180                 185                 190
Cys Lys Glu Val Ser Ala Ala Pro Ala Ile Cys Asn Gly Met Leu Gln
        195                 200                 205
Gly Ile Leu Ser Phe Ala Asp Gly Cys Val Leu Arg Ala Asp Val Gly
    210                 215                 220
Ile Tyr Ala Lys Ile Phe Tyr Tyr Ile Pro Trp Ile Glu Asn Val Ile
225                 230                 235                 240
Gln Asn Asn


      <210> 40
      <211> 483
      <212> PRT
      <213> Homo sapiens

      <400> 40
Met Tyr Pro Gly Trp Pro Gly Gln Gly Met Trp Ala Ser Gly Gln Arg
 1               5                  10                  15
Leu Pro Asp Glu Ala Phe Glu Ser Leu Thr Gln Leu Gln His Leu Cys
            20                  25                  30
Val Ala His Asn Lys Leu Ser Val Ala Pro Gln Phe Leu Pro Arg Ser
        35                  40                  45
Leu Arg Val Ala Asp Leu Ala Ala Asn Gln Val Met Glu Ile Phe Pro
    50                  55                  60
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Leu Thr Phe Gly Glu Lys Pro Ala Leu Arg Ser Val Tyr Leu His Asn
65 70 75 80
Asn Gln Leu Ser Asn Ala Gly Leu Pro Pro Asp Ala Phe Arg Gly Ser
85 90 95
Glu Ala Ile Ala Thr Leu Ser Leu Ser Asn Asn Gln Leu Ser Tyr Leu
100 105 110
Pro Pro Ser Leu Pro Pro Ser Leu Glu Arg Leu His Leu Gln Asn Asn
115 120 125
Leu Ile Ser Lys Val Pro Arg Gly Ala Leu Ser Arg Gln Thr Gln Leu
130 135 140
Arg Glu Leu Tyr Leu Gln His Asn Gln Leu Thr Asp Ser Gly Leu Asp
145 150 155 160
Ala Thr Thr Phe Ser Lys Leu His Ser Leu Glu Tyr Leu Asp Leu Ser
165 170 175
His Asn Gln Leu Thr Thr Val Pro Ala Gly Leu Pro Arg Thr Leu Ala
180 185 190
Ile Leu His Leu Gly Arg Asn Arg Ile Arg Gln Val Glu Ala Ala Arg
195 200 205
Leu His Gly Ala Arg Gly Leu Arg Tyr Leu Leu Leu Gln His Asn Gln
210 215 220
Leu Gly Ser Ser Gly Leu Pro Ala Gly Ala Leu Arg Pro Leu Arg Gly
225 230 235 240
Leu His Thr Leu His Leu Tyr Gly Asn Gly Leu Asp Arg Val Pro Pro
245 250 255
Ala Leu Pro Arg Arg Leu Arg Ala Leu Val Leu Pro His Asn His Val
260 265 270
Ala Ala Leu Gly Ala Arg Asp Leu Val Ala Thr Pro Gly Leu Thr Glu
275 280 285
Leu Asn Leu Ala Tyr Asn Arg Leu Ala Ser Ala Arg Val His His Arg
290 295 300
Ala Phe Arg Arg Leu Arg Ala Leu Arg Ser Leu Asp Leu Ala Gly Asn
305 310 315 320
Gln Leu Thr Arg Leu Pro Met Gly Leu Pro Thr Gly Leu Arg Thr Leu
325 330 335
Gln Leu Gln Arg Asn Gln Leu Arg Met Leu Glu Pro Glu Pro Leu Ala
340 345 350
Gly Leu Asp Gln Leu Arg Glu Leu Ser Leu Ala His Asn Arg Leu Arg
355 360 365
Val Gly Asp Ile Gly Pro Gly Thr Trp His Glu Leu Gln Ala Leu Gln
370 375 380
Met Leu Asp Leu Ser His Asn Glu Leu Ser Phe Val Pro Pro Asp Leu
385 390 395 400
Pro Glu Ala Leu Glu Glu Leu His Leu Glu Gly Asn Arg Ile Gly His
405 410 415
Val Gly Pro Glu Ala Phe Leu Ser Thr Pro Arg Leu Arg Ala Leu Phe
420 425 430
Leu Arg Ala Asn Arg Leu His Met Thr Ser Ile Ala Ala Glu Ala Phe
435 440 445
Leu Gly Leu Pro Asn Leu Arg Val Val Asp Thr Ala Gly Asn Pro Glu
450 455 460
Gln Val Leu Ile Arg Leu Pro Pro Thr Thr Pro Arg Gly Pro Arg Ala
465 470 475 480
Gly Gly Pro

<210> 41
<211> 605
<212> PRT
<213> Homo sapiens

<400> 41

Met Ala Glu Ser Gly Leu Ala Met Glu Gly Met Leu Gln Ser Pro Trp
1 5 10 15
Arg Pro Cys Ala Gln Pro Gly Asp Thr Leu Thr Leu Pro Pro Pro Gln
20 25 30
Trp Pro Ser Leu Leu Leu Leu Leu Leu Leu Pro Gly Pro Pro Pro Val
35 40 45
Ala Gly Leu Glu Asp Ala Ala Phe Pro His Leu Gly Glu Ser Leu Gln
50 55 60
Pro Leu Pro Arg Ala Cys Pro Leu Arg Cys Ser Cys Pro Arg Val Asp
65 70 75 80
Thr Val Asp Cys Asp Gly Leu Asp Leu Arg Val Phe Pro Asp Asn Ile
85 90 95
Thr Arg Ala Ala Gln His Leu Ser Leu Gln Asn Asn Gln Leu Gln Glu
100 105 110
Leu Pro Tyr Asn Glu Leu Ser Arg Leu Ser Gly Leu Arg Thr Leu Asn
115 120 125
Leu His Asn Asn Leu Ile Ser Ser Glu Gly Leu Pro Asp Glu Ala Phe
130 135 140
Glu Ser Leu Thr Gln Leu Gln His Leu Cys Val Ala His Asn Lys Leu
145 150 155 160
Ser Val Ala Pro Gln Phe Leu Pro Arg Ser Leu Arg Val Ala Asp Leu
165 170 175
Ala Ala Asn Gln Val Met Glu Ile Phe Pro Leu Thr Phe Gly Glu Lys
180 185 190
Pro Ala Leu Arg Ser Val Tyr Leu His Asn Asn Gln Leu Ser Asn Ala
195 200 205
Gly Leu Pro Pro Asp Ala Phe Arg Gly Ser Glu Ala Ile Ala Thr Leu
210 215 220
Ser Leu Ser Asn Asn Gln Leu Ser Tyr Leu Pro Pro Ser Leu Pro Pro
225 230 235 240
Ser Leu Glu Arg Leu His Leu Gln Asn Asn Leu Ile Ser Lys Val Pro
245 250 255
Arg Gly Ala Leu Ser Arg Gln Thr Gln Leu Arg Glu Leu Tyr Leu Gln
260 265 270
His Asn Gln Leu Thr Asp Ser Gly Leu Asp Ala Thr Thr Phe Ser Lys
275 280 285
Leu His Ser Leu Glu Tyr Leu Asp Leu Ser His Asn Gln Leu Thr Thr
290 295 300
Val Pro Ala Gly Leu Pro Arg Thr Leu Ala Ile Leu His Leu Gly Arg
305 310 315 320
Asn Arg Ile Arg Gln Val Glu Ala Ala Arg Leu His Gly Ala Arg Gly
325 330 335
Leu Arg Tyr Leu Leu Leu Gln His Asn Gln Leu Gly Ser Ser Gly Leu
340 345 350
Pro Ala Gly Ala Leu Arg Pro Leu Arg Gly Leu His Thr Leu His Leu
355 360 365
Tyr Gly Asn Gly Leu Asp Arg Val Pro Pro Ala Leu Pro Arg Arg Leu
370 375 380
Arg Ala Leu Val Leu Pro His Asn His Val Ala Ala Leu Gly Ala Arg
385 390 395 400
Asp Leu Val Ala Thr Pro Gly Leu Thr Glu Leu Asn Leu Ala Tyr Asn
405 410 415
Arg Leu Ala Ser Ala Arg Val His His Arg Ala Phe Arg Arg Leu Arg
420 425 430
Ala Leu Arg Ser Leu Asp Leu Ala Gly Asn Gln Leu Thr Arg Leu Pro
435 440 445
Met Gly Leu Pro Thr Gly Leu Arg Thr Leu Gln Leu Gln Arg Asn Gln

450 455 460
Leu Arg Met Leu Glu Pro Glu Pro Leu Ala Gly Leu Asp Gln Leu Arg
465 470 475 480
Glu Leu Ser Leu Ala His Asn Arg Leu Arg Val Gly Asp Ile Gly Pro
485 490 495
Gly Thr Trp His Glu Leu Gln Ala Leu Gln Met Leu Asp Leu Ser His
500 505 510
Asn Glu Leu Ser Phe Val Pro Pro Asp Leu Pro Glu Ala Leu Glu Glu
515 520 525
Leu His Leu Glu Gly Asn Arg Ile Gly His Val Gly Pro Glu Ala Phe
530 535 540
Leu Ser Thr Pro Arg Leu Arg Ala Leu Phe Leu Arg Ala Asn Arg Leu
545 550 555 560
His Met Thr Ser Ile Ala Ala Glu Ala Phe Leu Gly Leu Pro Asn Leu
565 570 575
Arg Val Val Asp Thr Ala Gly Asn Pro Glu Gln Val Leu Ile Arg Leu
580 585 590
Pro Pro Thr Thr Pro Arg Gly Pro Arg Ala Gly Gly Pro
595 600 605

<210> 42
<211> 1049
<212> PRT
<213> Homo sapiens

<400> 42
Met Val Thr Arg Glu Leu Phe Phe Leu Phe Ser Pro Gln Phe Phe Ser
1 5 10 15
Leu Asn Leu Arg Ser His Thr Arg Ser Thr Met Thr Ser Pro Gln Leu
20 25 30
Glu Trp Thr Leu Gln Thr Leu Leu Glu Gln Leu Asn Glu Asp Glu Leu
35 40 45
Lys Ser Phe Lys Ser Leu Leu Trp Ala Phe Pro Leu Glu Asp Val Leu
50 55 60
Gln Lys Thr Pro Trp Ser Glu Val Glu Glu Ala Asp Gly Lys Lys Leu
65 70 75 80
Ala Glu Ile Leu Val Asn Thr Ser Ser Glu Asn Trp Ile Arg Asn Ala
85 90 95
Thr Val Asn Ile Leu Glu Glu Met Asn Leu Thr Glu Leu Cys Lys Met
100 105 110
Ala Lys Ala Glu Met Met Glu Asp Gly Gln Val Gln Glu Ile Asp Asn
115 120 125
Pro Glu Leu Gly Asp Ala Glu Glu Asp Ser Glu Leu Ala Lys Pro Gly
130 135 140
Glu Lys Glu Gly Trp Arg Asn Ser Met Glu Lys Gln Ser Leu Val Trp
145 150 155 160
Lys Asn Thr Phe Trp Gln Gly Asp Ile Asp Asn Phe His Asp Asp Val
165 170 175
Thr Leu Arg Asn Gln Arg Phe Ile Pro Phe Leu Asn Pro Arg Thr Pro
180 185 190
Arg Lys Leu Thr Pro Tyr Thr Val Val Leu His Gly Pro Ala Gly Val
195 200 205
Gly Lys Thr Thr Leu Ala Lys Lys Cys Met Leu Asp Trp Thr Asp Cys
210 215 220
Asn Leu Ser Pro Thr Leu Arg Tyr Ala Phe Tyr Leu Ser Cys Lys Glu
225 230 235 240
Leu Ser Arg Met Gly Pro Cys Ser Phe Ala Glu Leu Ile Ser Lys Asp
245 250 255
Trp Pro Glu Leu Gln Asp Asp Ile Pro Ser Ile Leu Ala Gln Ala Gln

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                260                 265                 270
Arg Ile Leu Phe Val Val Asp Gly Leu Asp Glu Leu Lys Val Pro Pro
            275                 280                 285
Gly Ala Leu Ile Gln Asp Ile Cys Gly Asp Trp Glu Lys Lys Lys Pro
    290                 295                 300
Val Pro Val Leu Leu Gly Ser Leu Leu Lys Arg Lys Met Leu Pro Arg
305                 310                 315                 320
Ala Ala Leu Leu Val Thr Thr Arg Pro Arg Ala Leu Arg Asp Leu Gln
                325                 330                 335
Leu Leu Ala Gln Gln Pro Ile Tyr Val Arg Val Glu Gly Phe Leu Glu
            340                 345                 350
Glu Asp Arg Arg Ala Tyr Phe Leu Arg His Phe Gly Asp Glu Asp Gln
        355                 360                 365
Ala Met Arg Ala Phe Glu Leu Met Arg Ser Asn Ala Ala Leu Phe Gln
    370                 375                 380
Leu Gly Ser Ala Pro Ala Val Cys Trp Ile Val Cys Thr Thr Leu Lys
385                 390                 395                 400
Leu Gln Met Glu Lys Gly Glu Asp Pro Val Pro Thr Cys Leu Thr Arg
                405                 410                 415
Thr Gly Leu Phe Leu Arg Phe Leu Cys Ser Arg Phe Pro Gln Gly Ala
            420                 425                 430
Gln Leu Arg Gly Ala Leu Arg Thr Leu Ser Leu Leu Ala Ala Gln Gly
        435                 440                 445
Leu Trp Ala Gln Met Ser Val Phe His Arg Glu Asp Leu Glu Arg Leu
    450                 455                 460
Gly Val Gln Glu Ser Asp Leu Arg Leu Phe Leu Asp Gly Asp Ile Leu
465                 470                 475                 480
Arg Gln Asp Arg Val Ser Lys Gly Cys Tyr Ser Phe Ile His Leu Ser
                485                 490                 495
Phe Gln Gln Phe Leu Thr Ala Leu Phe Tyr Ala Leu Glu Lys Glu Glu
            500                 505                 510
Gly Glu Asp Arg Asp Gly His Ala Trp Asp Ile Gly Asp Val Gln Lys
        515                 520                 525
Leu Leu Ser Gly Glu Glu Arg Leu Lys Asn Pro Asp Leu Ile Gln Val
    530                 535                 540
Gly His Phe Leu Phe Gly Leu Ala Asn Glu Lys Arg Ala Lys Glu Leu
545                 550                 555                 560
Glu Ala Thr Phe Gly Cys Arg Met Ser Pro Asp Ile Lys Gln Glu Leu
                565                 570                 575
Leu Gln Cys Lys Ala His Leu His Ala Asn Lys Pro Leu Ser Val Thr
            580                 585                 590
Asp Leu Lys Glu Val Leu Gly Cys Leu Tyr Glu Ser Gln Glu Glu Glu
        595                 600                 605
Leu Ala Lys Val Val Val Ala Pro Phe Lys Glu Ile Ser Ile His Leu
    610                 615                 620
Thr Asn Thr Ser Glu Val Met His Cys Ser Phe Ser Leu Lys His Cys
625                 630                 635                 640
Gln Asp Leu Gln Lys Leu Ser Leu Gln Val Ala Lys Gly Val Phe Leu
                645                 650                 655
Glu Asn Tyr Met Asp Phe Glu Leu Asp Ile Glu Phe Glu Ser Ser Asn
            660                 665                 670
Ser Asn Leu Lys Phe Leu Glu Val Lys Gln Ser Phe Leu Ser Asp Ser
        675                 680                 685
Ser Val Arg Ile Leu Cys Asp His Val Thr Arg Ser Thr Cys His Leu
    690                 695                 700
Gln Lys Val Glu Ile Lys Asn Val Thr Pro Asp Thr Ala Tyr Arg Asp
705                 710                 715                 720
Phe Cys Leu Ala Phe Ile Gly Lys Lys Thr Leu Thr His Leu Thr Leu
                725                 730                 735
```

Ala Gly His Ile Glu Trp Glu Arg Thr Met Met Leu Met Leu Cys Asp
740 745 750
Leu Leu Arg Asn His Lys Cys Asn Leu Gln Tyr Leu Arg Leu Gly Gly
755 760 765
His Cys Ala Thr Pro Glu Gln Trp Ala Glu Phe Phe Tyr Val Leu Lys
770 775 780
Ala Asn Gln Ser Leu Lys His Leu Arg Leu Ser Ala Asn Val Leu Leu
785 790 795 800
Asp Glu Gly Ala Met Leu Leu Tyr Lys Thr Met Thr Arg Pro Lys His
805 810 815
Phe Leu Gln Met Leu Ser Leu Glu Asn Cys Arg Leu Thr Glu Ala Ser
820 825 830
Cys Lys Asp Leu Ala Ala Val Leu Val Val Ser Lys Lys Leu Thr His
835 840 845
Leu Cys Leu Ala Lys Asn Pro Ile Gly Asp Thr Gly Val Lys Phe Leu
850 855 860
Cys Glu Gly Leu Ser Tyr Pro Asp Cys Lys Leu Gln Thr Leu Val Leu
865 870 875 880
Val Ser Cys Ser Ala Thr Thr Gln Gln Trp Ala Asp Leu Ser Leu Ala
885 890 895
Leu Glu Val Asn Gln Ser Leu Thr Cys Val Asn Leu Ser Asp Asn Glu
900 905 910
Leu Leu Asp Glu Gly Ala Lys Leu Leu Tyr Thr Thr Leu Arg His Pro
915 920 925
Lys Cys Phe Leu Gln Arg Leu Ser Leu Glu Asn Cys His Leu Thr Glu
930 935 940
Ala Asn Cys Lys Asp Leu Ala Ala Val Leu Val Val Ser Arg Glu Leu
945 950 955 960
Thr His Leu Cys Leu Ala Lys Asn Pro Ile Gly Asn Thr Gly Val Lys
965 970 975
Phe Leu Cys Glu Gly Leu Arg Tyr Pro Glu Cys Lys Leu Gln Thr Leu
980 985 990
Val Leu Gln Gln Cys Ser Ile Thr Lys Leu Gly Cys Arg Tyr Leu Ser
995 1000 1005
Glu Ala Leu Gln Glu Ala Cys Ser Leu Thr Asn Leu Asp Leu Ser Ile
1010 1015 1020
Asn Gln Ile Ala Arg Gly Leu Trp Ile Leu Cys Gln Ala Leu Glu Asn
1025 1030 1035 1040
Pro Asn Cys Asn Leu Lys His Leu Arg
1045

<210> 43
<211> 1062
<212> PRT
<213> Homo sapiens

<400> 43
Met Val Ser Ser Ala Gln Met Gly Phe Asn Leu Gln Ala Leu Leu Glu
1 5 10 15
Gln Leu Ser Gln Asp Glu Leu Ser Lys Phe Lys Tyr Leu Ile Thr Thr
20 25 30
Phe Ser Leu Ala His Glu Leu Gln Lys Ile Pro His Lys Glu Val Asp
35 40 45
Lys Ala Asp Gly Lys Gln Leu Val Glu Ile Leu Thr Thr His Cys Asp
50 55 60
Ser Tyr Trp Val Glu Met Ala Ser Leu Gln Val Phe Glu Lys Met His
65 70 75 80
Arg Met Asp Leu Ser Glu Arg Ala Lys Asp Glu Val Arg Glu Ala Ala
85 90 95

Leu Lys Ser Phe Asn Lys Arg Lys Pro Leu Ser Leu Gly Ile Thr Arg
100 105 110
Lys Glu Arg Pro Pro Leu Asp Val Asp Glu Met Leu Glu Arg Phe Lys
115 120 125
Thr Glu Ala Gln Ala Phe Thr Glu Thr Lys Gly Asn Val Ile Cys Leu
130 135 140
Gly Lys Glu Val Phe Lys Gly Lys Lys Pro Asp Lys Asp Asn Arg Cys
145 150 155 160
Arg Tyr Ile Leu Lys Thr Lys Phe Arg Glu Met Trp Lys Ser Trp Pro
165 170 175
Gly Asp Ser Lys Glu Val Gln Val Met Ala Glu Arg Tyr Lys Met Leu
180 185 190
Ile Pro Phe Ser Asn Pro Arg Val Leu Pro Gly Pro Phe Ser Tyr Thr
195 200 205
Val Val Leu Tyr Gly Pro Ala Gly Leu Gly Lys Thr Thr Leu Ala Gln
210 215 220
Lys Leu Met Leu Asp Trp Ala Glu Asp Asn Leu Ile His Lys Phe Lys
225 230 235 240
Tyr Ala Phe Tyr Leu Ser Cys Arg Glu Leu Ser Arg Leu Gly Pro Cys
245 250 255
Ser Phe Ala Glu Leu Val Phe Arg Asp Trp Pro Glu Leu Gln Asp Asp
260 265 270
Ile Pro His Ile Leu Ala Gln Ala Arg Lys Ile Leu Phe Val Ile Asp
275 280 285
Gly Phe Asp Glu Leu Gly Ala Ala Pro Gly Ala Leu Ile Glu Asp Ile
290 295 300
Cys Gly Asp Trp Glu Lys Lys Lys Pro Val Pro Val Leu Leu Gly Ser
305 310 315 320
Leu Leu Asn Arg Val Met Leu Pro Lys Ala Ala Leu Leu Val Thr Thr
325 330 335
Arg Pro Arg Ala Leu Arg Asp Leu Arg Ile Leu Ala Glu Glu Pro Ile
340 345 350
Tyr Ile Arg Val Glu Gly Phe Leu Glu Glu Asp Arg Arg Ala Tyr Phe
355 360 365
Leu Arg His Phe Gly Asp Glu Asp Gln Ala Met Arg Ala Phe Glu Leu
370 375 380
Met Arg Ser Asn Ala Ala Leu Phe Gln Leu Gly Ser Ala Pro Ala Val
385 390 395 400
Cys Trp Ile Val Cys Thr Thr Leu Lys Leu Gln Met Glu Lys Gly Glu
405 410 415
Asp Pro Val Pro Thr Cys Leu Thr Arg Thr Gly Leu Phe Leu Arg Phe
420 425 430
Leu Cys Ser Arg Phe Pro Gln Gly Ala Gln Leu Arg Gly Ala Leu Arg
435 440 445
Thr Leu Ser Leu Leu Ala Ala Gln Gly Leu Trp Ala Gln Thr Ser Val
450 455 460
Leu His Arg Glu Asp Leu Glu Arg Leu Gly Val Gln Glu Ser Asp Leu
465 470 475 480
Arg Leu Phe Leu Asp Gly Asp Ile Leu Arg Gln Asp Arg Val Ser Lys
485 490 495
Gly Cys Tyr Ser Phe Ile His Leu Ser Phe Gln Gln Phe Leu Thr Ala
500 505 510
Leu Phe Tyr Thr Leu Glu Lys Glu Glu Glu Glu Asp Arg Asp Gly His
515 520 525
Thr Trp Asp Ile Gly Asp Val Gln Lys Leu Leu Ser Gly Val Glu Arg
530 535 540
Leu Arg Asn Pro Asp Leu Ile Gln Ala Gly Tyr Tyr Ser Phe Gly Leu
545 550 555 560
Ala Asn Glu Lys Arg Ala Lys Glu Leu Glu Ala Thr Phe Gly Cys Arg

565 570 575
Met Ser Pro Asp Ile Lys Gln Glu Leu Leu Arg Cys Asp Ile Ser Cys
580 585 590
Lys Gly Gly His Ser Thr Val Thr Asp Leu Gln Glu Leu Leu Gly Cys
595 600 605
Leu Tyr Glu Ser Gln Glu Glu Glu Leu Val Lys Glu Val Met Ala Gln
610 615 620
Phe Lys Glu Ile Ser Leu His Leu Asn Ala Val Asp Val Val Pro Ser
625 630 635 640
Ser Phe Cys Val Lys His Cys Arg Asn Leu Gln Lys Met Ser Leu Gln
645 650 655
Val Ile Lys Glu Asn Leu Pro Glu Asn Val Thr Ala Ser Glu Ser Asp
660 665 670
Ala Glu Val Glu Arg Ser Gln Asp Asp Gln His Met Leu Pro Phe Trp
675 680 685
Thr Asp Leu Cys Ser Ile Phe Gly Ser Asn Lys Asp Leu Met Gly Leu
690 695 700
Ala Ile Asn Asp Ser Phe Leu Ser Ala Ser Leu Val Arg Ile Leu Cys
705 710 715 720
Glu Gln Ile Ala Ser Asp Thr Cys His Leu Gln Arg Val Val Phe Lys
725 730 735
Asn Ile Ser Pro Ala Asp Ala His Arg Asn Leu Cys Leu Ala Leu Arg
740 745 750
Gly His Lys Thr Val Thr Tyr Leu Thr Leu Gln Gly Asn Asp Gln Asp
755 760 765
Asp Met Phe Pro Ala Leu Cys Glu Val Leu Arg His Pro Glu Cys Asn
770 775 780
Leu Arg Tyr Leu Gly Leu Val Ser Cys Ser Ala Thr Thr Gln Gln Trp
785 790 795 800
Ala Asp Leu Ser Leu Ala Leu Glu Val Asn Gln Ser Leu Thr Cys Val
805 810 815
Asn Leu Ser Asp Asn Glu Leu Leu Asp Glu Gly Ala Lys Leu Leu Tyr
820 825 830
Thr Thr Leu Arg His Pro Lys Cys Phe Leu Gln Arg Leu Ser Leu Glu
835 840 845
Asn Cys His Leu Thr Glu Ala Asn Cys Lys Asp Leu Ala Ala Val Leu
850 855 860
Val Val Ser Arg Glu Leu Thr His Leu Cys Leu Ala Lys Asn Pro Ile
865 870 875 880
Gly Asn Thr Gly Val Lys Phe Leu Cys Glu Gly Leu Arg Tyr Pro Glu
885 890 895
Cys Lys Leu Gln Thr Leu Val Leu Trp Asn Cys Asp Ile Thr Ser Asp
900 905 910
Gly Cys Cys Asp Leu Thr Lys Leu Leu Gln Glu Lys Ser Ser Leu Leu
915 920 925
Cys Leu Asp Leu Gly Leu Asn His Ile Gly Val Lys Gly Met Lys Phe
930 935 940
Leu Cys Glu Ala Leu Arg Lys Pro Leu Cys Asn Leu Arg Cys Leu Trp
945 950 955 960
Leu Trp Gly Cys Ser Ile Pro Pro Phe Ser Cys Glu Asp Leu Cys Ser
965 970 975
Ala Leu Ser Cys Asn Gln Ser Leu Val Thr Leu Asp Leu Gly Gln Asn
980 985 990
Pro Leu Gly Ser Ser Gly Val Lys Met Leu Phe Glu Thr Leu Thr Cys
995 1000 1005
Ser Ser Gly Thr Leu Arg Thr Leu Arg Leu Lys Ile Asp Asp Phe Asn
1010 1015 1020
Asp Glu Leu Asn Lys Leu Leu Glu Glu Ile Glu Glu Lys Asn Pro Gln
1025 1030 1035 1040

Leu Ile Ile Asp Thr Glu Lys His His Pro Trp Ala Glu Arg Pro Ser
1045 1050 1055
Ser His Asp Phe Met Ile
1060

<210> 44
<211> 353
<212> PRT
<213> Homo sapiens

<400> 44
Met Thr Ile Phe His Pro Ile Thr Ser Ser Ile Gly Gln Pro Gly Cys
1 5 10 15
Gly Pro Lys Cys Lys Glu Thr Pro Leu Glu Leu Val Phe Val Ile Asp
20 25 30
Ser Ser Glu Ser Val Gly Pro Glu Asn Phe Gln Ile Ile Lys Asn Phe
35 40 45
Val Lys Thr Met Ala Asp Arg Val Ala Leu Asp Leu Ala Thr Ala Arg
50 55 60
Ile Gly Ile Ile Asn Tyr Ser His Lys Val Glu Lys Val Ala Asn Leu
65 70 75 80
Lys Gln Phe Ser Ser Lys Asp Asp Phe Lys Leu Ala Val Asp Asn Met
85 90 95
Gln Tyr Leu Gly Glu Gly Thr Tyr Thr Ala Thr Ala Leu Gln Ala Ala
100 105 110
Asn Asp Met Phe Glu Asp Ala Arg Pro Gly Val Lys Lys Val Ala Leu
115 120 125
Val Ile Thr Asp Gly Gln Thr Asp Ser Arg Asp Lys Glu Lys Leu Thr
130 135 140
Glu Val Val Lys Asn Ala Ser Asp Thr Asn Val Glu Ile Phe Val Ile
145 150 155 160
Gly Val Val Lys Lys Asn Asp Pro Asn Phe Glu Ile Phe His Lys Glu
165 170 175
Met Asn Leu Ile Ala Thr Asp Pro Glu His Val Tyr Gln Phe Asp Asp
180 185 190
Phe Phe Thr Leu Gln Asp Thr Leu Lys Gln Lys Leu Phe Gln Lys Ile
195 200 205
Cys Glu Asp Phe Asp Ser Tyr Leu Val Gln Ile Phe Gly Ser Ser Ser
210 215 220
Pro Gln Pro Gly Phe Gly Met Ser Gly Glu Glu Leu Ser Glu Ser Thr
225 230 235 240
Pro Glu Pro Gln Lys Glu Ile Ser Glu Ser Leu Ser Val Thr Arg Asp
245 250 255
Gln Asp Glu Asp Asp Lys Ala Pro Glu Pro Thr Trp Ala Asp Asp Leu
260 265 270
Pro Ala Thr Thr Ser Ser Glu Ala Thr Thr Thr Pro Arg Pro Leu Leu
275 280 285
Ser Thr Pro Val Asp Gly Ala Glu Asp Pro Arg Cys Leu Glu Ala Leu
290 295 300
Lys Pro Gly Asn Cys Gly Glu Tyr Val Val Arg Trp Tyr Tyr Asp Lys
305 310 315 320
Gln Val Asn Ser Cys Ala Arg Phe Trp Phe Ser Gly Cys Asn Gly Ser
325 330 335
Gly Asn Arg Phe Asn Ser Glu Lys Glu Cys Gln Glu Thr Cys Ile Gln
340 345 350
Gly

<210> 45

<211> 448
<212> PRT
<213> Homo sapiens

<400> 45

```
Met His Glu Val Ile Glu Ser Asp Tyr Glu Gly Arg Asp Lys Thr Leu
1               5                   10                  15
Ser Cys Leu Val Val Gly Val Cys Asp Tyr Ser Thr Arg Met Leu Gly
            20                  25                  30
Arg Asn Asp His Thr Ala Val Thr Gly Gln Gln Gly Ala Trp Ser Glu
        35                  40                  45
Ser Ala Ser Leu Asp His Ser Pro Ile Leu Ser Phe Leu Pro Gln Glu
    50                  55                  60
Phe Pro Ala Asp Arg Asp Gly Ser Leu Ala Leu His Ser Thr Tyr Glu
65                  70                  75                  80
Ser Leu Arg Leu Ser Ala Ser Ser Trp Thr Val Asn Pro Leu Arg Gly
                85                  90                  95
Ile Asn Met Met Pro Ser Ser Leu Ala Pro Ser Ser Gln Gly Cys Gly
            100                 105                 110
Pro Lys Cys Lys Glu Thr Pro Leu Glu Leu Val Phe Val Ile Asp Ser
        115                 120                 125
Ser Glu Ser Val Gly Pro Glu Asn Phe Gln Ile Ile Lys Asn Phe Val
    130                 135                 140
Lys Thr Met Ala Asp Arg Val Ala Leu Asp Leu Ala Thr Ala Arg Ile
145                 150                 155                 160
Gly Ile Ile Asn Tyr Ser His Lys Val Glu Lys Val Ala Asn Leu Lys
                165                 170                 175
Gln Phe Ser Ser Lys Asp Asp Phe Lys Leu Ala Val Asp Asn Met Gln
            180                 185                 190
Tyr Leu Gly Glu Gly Thr Tyr Thr Ala Thr Ala Leu Gln Ala Ala Asn
        195                 200                 205
Asp Met Phe Glu Asp Ala Arg Pro Gly Val Lys Lys Val Ala Leu Val
    210                 215                 220
Ile Thr Asp Gly Gln Thr Asp Ser Arg Asp Lys Glu Lys Leu Thr Glu
225                 230                 235                 240
Val Val Lys Asn Ala Ser Asp Thr Asn Val Glu Ile Phe Val Ile Gly
                245                 250                 255
Val Val Lys Lys Asn Asp Pro Asn Phe Glu Ile Phe His Lys Glu Met
            260                 265                 270
Asn Leu Ile Ala Thr Asp Pro Glu His Val Tyr Gln Phe Asp Asp Phe
        275                 280                 285
Phe Thr Leu Gln Asp Thr Leu Lys Gln Lys Leu Phe Gln Lys Ile Cys
    290                 295                 300
Glu Asp Phe Asp Ser Tyr Leu Val Gln Ile Phe Gly Ser Ser Ser Pro
305                 310                 315                 320
Gln Pro Gly Phe Gly Met Ser Gly Glu Glu Leu Ser Glu Ser Thr Pro
                325                 330                 335
Glu Pro Gln Lys Glu Ile Ser Glu Ser Leu Ser Val Thr Arg Asp Gln
            340                 345                 350
Asp Glu Asp Asp Lys Ala Pro Glu Pro Thr Trp Ala Asp Asp Leu Pro
        355                 360                 365
Ala Thr Thr Ser Ser Glu Ala Thr Thr Thr Pro Arg Pro Leu Leu Ser
    370                 375                 380
Thr Pro Val Asp Gly Ala Glu Asp Pro Arg Cys Leu Glu Ala Leu Lys
385                 390                 395                 400
Pro Gly Asn Cys Gly Glu Tyr Val Val Arg Trp Tyr Tyr Asp Lys Gln
                405                 410                 415
Val Asn Ser Cys Ala Arg Phe Trp Phe Ser Gly Cys Asn Gly Ser Gly
            420                 425                 430
```

Asn Arg Phe Asn Ser Glu Lys Glu Cys Gln Glu Thr Cys Ile Gln Gly
435 440 445

<210> 46
<211> 493
<212> PRT
<213> Homo sapiens

<400> 46
Met Leu Pro Ala Ala Pro Ser Gly Cys Pro Gln Leu Cys Arg Cys Glu
1 5 10 15
Gly Arg Leu Leu Tyr Cys Glu Ala Leu Asn Leu Thr Glu Ala Pro His
20 25 30
Asn Leu Ser Gly Leu Leu Gly Leu Ser Leu Arg Tyr Asn Ser Leu Ser
35 40 45
Glu Leu Arg Ala Gly Gln Phe Thr Gly Leu Met Gln Leu Thr Trp Leu
50 55 60
Tyr Leu Asp His Asn His Ile Cys Ser Val Gln Gly Asp Ala Phe Gln
65 70 75 80
Lys Leu Arg Arg Val Lys Glu Leu Thr Leu Ser Ser Asn Gln Ile Thr
85 90 95
Gln Leu Pro Asn Thr Thr Phe Arg Pro Met Pro Asn Leu Arg Ser Val
100 105 110
Asp Leu Ser Tyr Asn Lys Leu Gln Ala Leu Ala Pro Asp Leu Phe His
115 120 125
Gly Leu Arg Lys Leu Thr Thr Leu His Met Arg Ala Asn Ala Ile Gln
130 135 140
Phe Val Pro Val Arg Ile Phe Gln Asp Cys Arg Ser Leu Lys Phe Leu
145 150 155 160
Asp Ile Gly Tyr Asn Gln Leu Lys Ser Leu Ala Arg Asn Ser Phe Ala
165 170 175
Gly Leu Phe Lys Leu Thr Glu Leu His Leu Glu His Asn Asp Leu Val
180 185 190
Lys Val Asn Phe Ala His Phe Pro Arg Leu Ile Ser Leu His Ser Leu
195 200 205
Cys Leu Arg Arg Asn Lys Val Ala Ile Val Val Ser Ser Leu Asp Trp
210 215 220
Val Trp Asn Leu Glu Lys Met Asp Leu Ser Gly Asn Glu Ile Glu Tyr
225 230 235 240
Met Glu Pro His Val Phe Glu Thr Val Pro His Leu Gln Ser Leu Gln
245 250 255
Leu Asp Ser Asn Arg Leu Thr Tyr Ile Glu Pro Arg Ile Leu Asn Ser
260 265 270
Trp Lys Ser Leu Thr Ser Ile Thr Leu Ala Gly Asn Leu Trp Asp Cys
275 280 285
Gly Arg Asn Val Cys Ala Leu Ala Ser Trp Leu Asn Asn Phe Gln Gly
290 295 300
Arg Tyr Asp Gly Asn Leu Gln Cys Ala Ser Pro Glu Tyr Ala Gln Gly
305 310 315 320
Glu Asp Val Leu Asp Ala Val Tyr Ala Phe His Leu Cys Glu Asp Gly
325 330 335
Ala Glu Pro Thr Ser Gly His Leu Leu Ser Ala Val Thr Asn Arg Ser
340 345 350
Asp Leu Gly Pro Pro Ala Arg Arg Ala Thr Thr Ala Ser Arg Thr Gly
355 360 365
Gly Glu Gly Gln His Asp Gly Thr Phe Lys Pro Ala Thr Gly Gly Phe
370 375 380
Pro Ala Gly Glu His Ala Lys Asn Pro Val Gln Ile His Lys Val Val
385 390 395 400

Thr Gly Thr Met Ala Phe Ile Phe Ser Phe Leu Met Val Val Leu Val
405 410 415
Leu Tyr Val Ser Trp Lys Cys Phe Pro Ala Ser Leu Arg Gln Leu Arg
420 425 430
Gln Cys Phe Val Thr Gln Arg Arg Lys Gln Lys Gln Lys Gln Thr Met
435 440 445
His Gln Met Ala Ala Met Ser Ala Gln Glu Tyr Tyr Val Asp Tyr Lys
450 455 460
Pro Asn His Ile Glu Gly Ala Leu Val Ile Ile Asn Glu Tyr Gly Ser
465 470 475 480
Cys Thr Cys His Gln Gln Pro Ala Arg Glu Cys Glu Val
485 490

<210> 47
<211> 548
<212> PRT
<213> Homo sapiens

<400> 47
Met Pro Ala Leu Arg Pro Leu Leu Pro Leu Leu Leu Leu Leu Arg Leu
1 5 10 15
Thr Ser Gly Ala Gly Leu Leu Pro Gly Leu Gly Ser His Pro Gly Val
20 25 30
Cys Pro Asn Gln Leu Ser Pro Asn Leu Trp Val Asp Ala Gln Ser Thr
35 40 45
Cys Glu Arg Glu Cys Ser Arg Asp Gln Asp Cys Ala Ala Ala Glu Lys
50 55 60
Cys Cys Ile Asn Val Cys Gly Leu His Ser Cys Val Ala Ala Arg Phe
65 70 75 80
Pro Gly Ser Pro Ala Ala Pro Thr Thr Ala Ala Ser Cys Glu Gly Phe
85 90 95
Val Cys Pro Gln Gln Gly Ser Asp Cys Asp Ile Trp Asp Gly Gln Pro
100 105 110
Val Cys Arg Cys Arg Asp Arg Cys Glu Lys Glu Pro Ser Phe Thr Cys
115 120 125
Ala Ser Asp Gly Leu Thr Tyr Tyr Asn Arg Cys Tyr Met Asp Ala Glu
130 135 140
Ala Cys Leu Arg Gly Leu His Leu His Ile Val Pro Cys Lys His Val
145 150 155 160
Leu Ser Trp Pro Pro Ser Ser Pro Gly Pro Pro Glu Thr Thr Ala Arg
165 170 175
Pro Thr Pro Gly Ala Ala Pro Val Pro Pro Ala Leu Tyr Ser Ser Pro
180 185 190
Ser Pro Gln Ala Val Gln Val Gly Gly Thr Ala Ser Leu His Cys Asp
195 200 205
Val Ser Gly Arg Pro Pro Pro Ala Val Thr Trp Glu Lys Gln Ser His
210 215 220
Gln Arg Glu Asn Leu Ile Met Arg Pro Asp Gln Met Tyr Gly Asn Val
225 230 235 240
Val Val Thr Ser Ile Gly Gln Leu Val Leu Tyr Asn Ala Arg Pro Glu
245 250 255
Asp Ala Gly Leu Tyr Thr Cys Thr Ala Arg Asn Ala Ala Gly Leu Leu
260 265 270
Arg Ala Asp Phe Pro Leu Ser Val Val Gln Arg Glu Pro Ala Arg Asp
275 280 285
Ala Ala Pro Ser Ile Pro Ala Pro Ala Glu Cys Leu Pro Asp Val Gln
290 295 300
Ala Cys Thr Gly Pro Thr Ser Pro His Leu Val Leu Trp His Tyr Asp
305 310 315 320

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Pro Gln Arg Gly Gly Cys Met Thr Phe Pro Ala Arg Gly Cys Asp Gly
                325                 330                 335
Ala Ala Arg Gly Phe Glu Thr Tyr Glu Ala Cys Gln Gln Ala Cys Ala
            340                 345                 350
Arg Gly Pro Gly Asp Ala Cys Val Leu Pro Ala Val Gln Gly Pro Cys
        355                 360                 365
Arg Gly Trp Glu Pro Arg Trp Ala Tyr Ser Pro Leu Leu Gln Gln Cys
    370                 375                 380
His Pro Phe Val Tyr Gly Gly Cys Glu Gly Asn Gly Asn Asn Phe His
385                 390                 395                 400
Ser Arg Glu Ser Cys Glu Asp Ala Cys Pro Val Pro Arg Thr Pro Pro
                405                 410                 415
Cys Arg Ala Cys Arg Leu Arg Ser Lys Leu Ala Leu Ser Leu Cys Arg
            420                 425                 430
Ser Asp Phe Ala Ile Val Gly Arg Leu Thr Glu Val Leu Glu Glu Pro
        435                 440                 445
Glu Ala Ala Gly Gly Ile Ala Arg Val Ala Leu Glu Asp Val Leu Lys
    450                 455                 460
Asp Asp Lys Met Gly Leu Lys Phe Leu Gly Thr Lys Tyr Leu Glu Val
465                 470                 475                 480
Thr Leu Ser Gly Met Asp Trp Ala Cys Pro Cys Pro Asn Met Thr Ala
                485                 490                 495
Gly Asp Gly Pro Leu Val Ile Met Gly Glu Val Arg Asp Gly Val Ala
            500                 505                 510
Val Leu Asp Ala Gly Ser Tyr Val Arg Ala Ala Ser Glu Lys Arg Val
        515                 520                 525
Lys Lys Ile Leu Glu Leu Leu Glu Lys Gln Ala Cys Glu Leu Leu Asn
    530                 535                 540
Arg Phe Gln Asp
545

     <210> 48
     <211> 286
     <212> PRT
     <213> Homo sapiens

     <400> 48
Met Ala Phe Val Ala Ile Val Val Ser Asn Phe Gly Leu Ser Gly Gln
 1               5                  10                  15
Pro His Gly Gly Phe Asn Ser Gln Asp Gln Asn Asp Gln Gly Pro Ser
            20                  25                  30
Val Pro Val Ser Leu Leu Asp Arg Thr Thr Gly Gly Gly Ser Ala Leu
        35                  40                  45
Cys Phe Leu Ala Gly Ile Asp Tyr Lys Thr Thr Thr Ile Leu Leu Asp
    50                  55                  60
Gly Arg Arg Val Lys Leu Glu Leu Trp Asp Thr Ser Gly Gln Gly Arg
65                  70                  75                  80
Phe Cys Thr Ile Phe Arg Ser Tyr Ser Arg Gly Ala Gln Gly Ile Leu
                85                  90                  95
Leu Val Tyr Asp Ile Thr Asn Arg Trp Ser Phe Asp Gly Ile Asp Arg
            100                 105                 110
Trp Ile Lys Glu Ile Asp Glu His Ala Pro Gly Val Pro Arg Ile Leu
        115                 120                 125
Val Gly Asn Arg Leu His Leu Ala Phe Lys Arg Gln Val Pro Thr Glu
    130                 135                 140
Gln Ala Arg Ala Tyr Ala Glu Lys Asn Cys Met Thr Phe Phe Glu Val
145                 150                 155                 160
Ser Pro Leu Cys Asn Phe Asn Val Ile Glu Ser Phe Thr Glu Leu Ser
                165                 170                 175
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Arg Ile Val Leu Met Arg His Gly Met Glu Lys Ile Trp Arg Pro Asn
180 185 190
Arg Val Phe Ser Leu Gln Asp Leu Cys Cys Arg Ala Ile Val Ser Cys
195 200 205
Thr Pro Val His Leu Ile Asp Lys Leu Pro Leu Pro Val Thr Ile Lys
210 215 220
Ser His Leu Lys Ser Phe Ser Met Ala Asn Gly Met Asn Ala Val Met
225 230 235 240
Met His Gly Arg Ser Tyr Ser Leu Ala Ser Gly Ala Gly Gly Gly Gly
245 250 255
Ser Lys Gly Asn Ser Leu Lys Arg Ser Lys Ser Ile Arg Pro Pro Gln
260 265 270
Ser Pro Pro Gln Asn Cys Ser Arg Ser Asn Cys Lys Ile Ser
275 280 285

<210> 49
<211> 172
<212> PRT
<213> Homo sapiens

<400> 49
Met Gly Ile Pro Ile Pro Ile Ile Pro His His Pro Gln Ala Arg Val
1 5 10 15
Ala Ser Pro Gln Ala Leu Met Asp Lys Trp Pro Trp Lys Ala Ser Ser
20 25 30
Ala Ala Pro Gly Phe Cys His His Pro Ser Thr Lys Trp Ser Arg Asp
35 40 45
Pro Gly Arg His Pro Glu Ser Pro His Arg Gly Gly Ser Gly Val His
50 55 60
Arg Arg Ser Arg Glu Pro Ala Pro His Pro Ala Ser Glu Glu Ser Ser
65 70 75 80
Phe Pro Trp Leu Glu Asp Pro Val Met Lys Tyr Val Gly Lys Gly Gly
85 90 95
Tyr Asn Cys Thr Leu Ser Lys Thr Glu Phe Leu Ser Phe Met Asn Ala
100 105 110
Glu Leu Ala Ala Phe Thr Lys Asn Gln Lys Asp Pro Gly Val Leu His
115 120 125
Arg Met Met Lys Lys Leu Gly Thr Asn Asn Asp Gly Gln Leu Asp Phe
130 135 140
Ser Glu Phe Leu Asn Leu Ile Gly Gly Leu Ala Met Ala Cys His Asp
145 150 155 160
Ser Phe Leu Lys Ala Val Pro Ser Gln Lys Arg Thr
165 170

<210> 50
<211> 103
<212> PRT
<213> Homo sapiens

<400> 50
Leu Gln Lys Ser Pro Ala Leu Gln Arg Leu Ser Ile Glu Ser Leu Ile
1 5 10 15
Ser Leu Phe Gln Lys Tyr Val Gly Lys Gly Gly Tyr Asn Cys Thr Leu
20 25 30
Ser Lys Thr Glu Phe Leu Ser Phe Met Asn Ala Glu Leu Ala Ala Phe
35 40 45
Thr Lys Asn Gln Lys Asp Pro Gly Val Leu His Arg Met Met Lys Lys
50 55 60
Leu Gly Thr Asn Asn Asp Gly Gln Leu Asp Phe Ser Glu Phe Leu Asn

```
65                  70                      75                      80
Leu Ile Gly Gly Leu Ala Met Ala Cys His Asp Ser Phe Leu Lys Ala
                85                      90                      95
Val Pro Ser Gln Lys Arg Thr
            100

      <210> 51
      <211> 753
      <212> PRT
      <213> Homo sapiens

      <400> 51
Met Arg Pro Val Ser Val Trp Gln Trp Ser Pro Trp Gly Leu Leu Leu
 1               5                  10                  15
Cys Leu Leu Cys Ser Ser Cys Leu Gly Ser Pro Ser Pro Ser Thr Gly
            20                  25                  30
Pro Glu Lys Lys Ala Gly Ser Gln Gly Leu Arg Phe Arg Leu Ala Gly
        35                  40                  45
Phe Pro Arg Lys Pro Tyr Glu Gly Arg Val Glu Ile Gln Arg Ala Gly
    50                  55                  60
Glu Trp Gly Thr Ile Cys Asp Asp Asp Phe Thr Leu Gln Ala Ala His
65                  70                  75                  80
Ile Leu Cys Arg Glu Leu Gly Phe Thr Glu Ala Thr Gly Trp Thr His
                85                  90                  95
Ser Ala Lys Tyr Gly Pro Gly Thr Gly Arg Ile Trp Leu Asp Asn Leu
            100                 105                 110
Ser Cys Ser Gly Thr Glu Gln Ser Val Thr Glu Cys Ala Ser Arg Gly
        115                 120                 125
Trp Gly Asn Ser Asp Cys Thr His Asp Glu Asp Ala Gly Val Ile Cys
    130                 135                 140
Lys Asp Gln Arg Leu Pro Gly Phe Ser Asp Ser Asn Val Ile Glu Val
145                 150                 155                 160
Glu His His Leu Gln Val Glu Glu Val Arg Ile Arg Pro Ala Val Gly
                165                 170                 175
Trp Gly Arg Arg Pro Leu Pro Val Thr Glu Gly Leu Val Glu Val Arg
            180                 185                 190
Leu Pro Asp Gly Trp Ser Gln Val Cys Asp Lys Gly Trp Ser Ala His
        195                 200                 205
Asn Ser His Val Val Cys Gly Met Leu Gly Phe Pro Ser Glu Lys Arg
    210                 215                 220
Val Asn Ala Ala Phe Tyr Arg Leu Leu Ala Gln Arg Gln Gln His Ser
225                 230                 235                 240
Phe Gly Leu His Gly Val Ala Cys Val Gly Thr Glu Ala His Leu Ser
                245                 250                 255
Leu Cys Ser Leu Glu Phe Tyr Arg Ala Asn Asp Thr Ala Arg Cys Pro
            260                 265                 270
Gly Gly Gly Pro Ala Val Val Ser Cys Val Pro Gly Pro Val Tyr Ala
        275                 280                 285
Ala Ser Ser Gly Gln Lys Lys Gln Gln Gln Ser Lys Pro Gln Gly Glu
    290                 295                 300
Ala Arg Val Arg Leu Lys Gly Gly Ala His Pro Gly Glu Gly Arg Val
305                 310                 315                 320
Glu Val Leu Lys Ala Ser Thr Trp Gly Thr Val Cys Asp Arg Lys Trp
                325                 330                 335
Asp Leu His Ala Ala Ser Val Val Cys Arg Glu Leu Gly Phe Gly Ser
            340                 345                 350
Ala Arg Glu Ala Leu Ser Gly Ala Arg Met Gly Gln Gly Met Gly Ala
        355                 360                 365
Ile His Leu Ser Glu Val Arg Cys Ser Gly Gln Glu Leu Ser Leu Trp
```

370 375 380
Lys Cys Pro His Lys Asn Ile Thr Ala Glu Asp Cys Ser His Ser Gln
385 390 395 400
Asp Ala Gly Val Arg Cys Asn Leu Pro Tyr Thr Gly Ala Glu Thr Arg
405 410 415
Ile Arg Leu Ser Gly Gly Arg Ser Gln His Glu Gly Arg Val Glu Val
420 425 430
Gln Ile Gly Gly Pro Gly Pro Leu Arg Trp Gly Leu Ile Cys Gly Asp
435 440 445
Asp Trp Gly Thr Leu Glu Ala Met Val Ala Cys Arg Gln Leu Gly Leu
450 455 460
Gly Tyr Ala Asn His Gly Leu Gln Glu Thr Trp Tyr Trp Asp Ser Gly
465 470 475 480
Asn Ile Thr Glu Val Val Met Ser Gly Val Arg Cys Thr Gly Thr Glu
485 490 495
Leu Ser Leu Asp Gln Cys Ala His His Gly Thr His Ile Thr Cys Lys
500 505 510
Arg Thr Gly Thr Arg Phe Thr Ala Gly Val Ile Cys Ser Glu Thr Ala
515 520 525
Ser Asp Leu Leu Leu His Ser Ala Leu Val Gln Glu Thr Ala Tyr Ile
530 535 540
Glu Asp Arg Pro Leu His Met Leu Tyr Cys Ala Ala Glu Glu Asn Cys
545 550 555 560
Leu Ala Ser Ser Ala Arg Ser Ala Asn Trp Pro Tyr Gly His Arg Arg
565 570 575
Leu Leu Arg Phe Ser Ser Gln Ile His Asn Leu Gly Arg Ala Asp Phe
580 585 590
Arg Pro Lys Ala Gly Arg His Ser Trp Val Trp His Glu Cys His Gly
595 600 605
His Tyr His Ser Met Asp Ile Phe Thr His Tyr Asp Ile Leu Thr Pro
610 615 620
Asn Gly Thr Lys Val Ala Glu Gly His Lys Ala Ser Phe Cys Leu Glu
625 630 635 640
Asp Thr Glu Cys Gln Glu Asp Val Ser Lys Arg Tyr Glu Cys Ala Asn
645 650 655
Phe Gly Glu Gln Gly Ile Thr Val Gly Cys Trp Asp Leu Tyr Arg His
660 665 670
Asp Ile Asp Cys Gln Trp Ile Asp Ile Thr Asp Val Lys Pro Gly Asn
675 680 685
Tyr Ile Leu Gln Val Val Ile Asn Pro Asn Phe Glu Val Ala Glu Ser
690 695 700
Asp Phe Thr Asn Asn Ala Met Lys Cys Asn Cys Lys Tyr Asp Gly His
705 710 715 720
Arg Ile Trp Val His Asn Cys His Ile Gly Asp Ala Phe Ser Glu Glu
725 730 735
Ala Asn Arg Arg Phe Glu Arg Tyr Pro Gly Gln Thr Ser Asn Gln Ile
740 745 750
Ile

<210> 52
<211> 114
<212> PRT
<213> Homo sapiens

<400> 52
Met Glu Ser Ala Ala Gln Leu Gly Pro Gln Val Pro Val Ala Leu Ser
1 5 10 15
Trp Met Arg Asp Gln Gly Gln Gly His Cys Ile Thr Thr Leu Cys Cys

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            20                         25                        30
Phe Pro Glu Arg Tyr Ala Gly Arg Asp His Asn Ser Cys Lys Leu Ser
        35                      40                      45
Gln Arg Gly Phe Leu Asn Phe Met Asn Thr Val Leu Val Ala Phe Thr
    50                      55                      60
Lys Asn Gln Lys Gly Ser Gly Ala Leu Asp Cys Met Met Lys Lys Leu
65                      70                      75                      80
Asp Phe Asn Cys Asp Gly Gln Asp Phe Gln Asp Phe Leu Ser Leu Thr
                85                      90                      95
Asp Gly Val Ala Val Ala Cys Pro Asp Ser Phe Ile Pro Ala Gly His
            100                     105                     110
Ala Pro


      <210> 53
      <211> 106
      <212> PRT
      <213> Homo sapiens

      <400> 53
Met Ala Lys Ile Ser Gly Cys Thr Glu Ile Ala Trp Trp Cys Ile Thr
1               5                   10                      15
Thr Leu Cys Cys Phe Pro Glu Arg Tyr Ala Gly Arg Asp His Asn Ser
            20                      25                      30
Cys Lys Leu Ser Gln Arg Gly Phe Leu Asn Phe Met Asn Thr Val Leu
        35                      40                      45
Val Ala Phe Thr Lys Asn Gln Lys Gly Ser Gly Ala Leu Asp Cys Met
    50                      55                      60
Met Lys Lys Leu Asp Phe Asn Cys Asp Gly Gln Leu Asp Phe Gln Asp
65                      70                      75                      80
Phe Leu Ser Leu Thr Asp Gly Val Ala Val Ala Cys Pro Asp Ser Phe
                85                      90                      95
Ile Pro Ala Gly His Ala His Glu Arg Ile
            100                     105

      <210> 54
      <211> 643
      <212> PRT
      <213> Homo sapiens

      <400> 54
Met Ala Leu Ala Gly Pro Cys Pro Ser Ser Thr Ala Ser Leu Leu Pro
1               5                   10                      15
Ser Thr Gln Ala Leu Pro Thr Ile Asn Ser Phe Leu Lys Ile Ala Ser
            20                      25                      30
Lys Pro Lys Ser Thr Leu Asp Arg Ala Val Gly Lys Ala Ser Ser Ile
        35                      40                      45
Leu Ala Leu Lys Ser Arg Ala Ser Ala Lys Arg Ser Val Leu Leu Pro
    50                      55                      60
Ile Leu Ala Leu Trp Ala Gly Ser Cys Ser Gly Gly Ala Pro Pro Thr
65                      70                      75                      80
Pro Met Gly Leu Ala Thr Leu Gln Leu Leu Pro Ser Pro Pro Gly Ala
                85                      90                      95
Pro Asp Gly Gln Leu Gln Pro Ile Pro Gly Ile Gly His Pro Asp Lys
            100                     105                     110
Pro Glu Ala Gly Lys Leu Asp Gln Leu Arg Asp Gln Pro Thr Pro Lys
        115                     120                     125
Gln Gly Ala Gln Gly Thr Pro Thr Gln Ser Pro Ser Thr Gly Trp Lys
    130                     135                     140
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Ala Leu Pro Arg Pro Gly Leu Ala Leu Arg Lys Glu Ser Pro Pro Val
145 150 155 160
Thr Leu Glu Gln Glu Gln Gly His Asn Lys Gly Leu Val Ala Glu Trp
165 170 175
Ala Gln Pro Gln Ala Thr Ala Ala Met Arg Ala Gly Ala Gly Lys Pro
180 185 190
Glu Ala Leu Lys Leu Arg Pro Trp Gln Ala Gly Arg Asp Pro Gln Ala
195 200 205
Gln Glu Gly Ala Ala Val Thr Glu Glu Asp Gln Gly Gln Arg Thr Gly
210 215 220
Gly Arg Glu Asp Lys Gly Arg Gly Leu Lys Pro Arg Arg Pro Pro Lys
225 230 235 240
Gly Thr Ser His Gln Pro Gly Leu Arg Ile Arg Arg Pro Gln Lys Asp
245 250 255
Arg Ser Arg Gly Gln Gly Gly Gly Gly Ser Thr Ser Lys Thr Pro Gly
260 265 270
His Gly Trp Lys Arg Pro Gly Ser Thr His Gly His Arg His Arg His
275 280 285
Ala Asp Leu Gly Thr Thr Gln Gln Ala Met Pro Ser Leu Pro Ala Ser
290 295 300
Cys Leu Leu Ala Gln Ala Val Ile Ala Cys Gly Asn Val Lys Met Lys
305 310 315 320
His Val Pro Ala Leu Thr His Pro Gly Leu Thr Thr Leu Tyr Leu Ala
325 330 335
Glu Asn Glu Ile Ala Lys Ile Pro Ala His Thr Phe Leu Gly Leu Pro
340 345 350
Asn Leu Glu Trp Leu Asp Leu Ser Lys Asn Lys Leu Asp Pro Arg Gly
355 360 365
Leu His Pro His Ala Phe Lys Asn Leu Met Arg Leu Lys Arg Leu Asn
370 375 380
Leu Val Gly Asn Ser Leu Thr Thr Val Pro Ala Leu Pro Ala Ser Leu
385 390 395 400
Gln Glu Leu Lys Leu Asn Asp Asn Leu Leu Gln Gly Leu Gln Gly Ser
405 410 415
Ser Phe Arg Gly Leu Ser Gln Leu Leu Thr Leu Glu Glu Leu His Leu
420 425 430
Gly Thr Asn Leu Ile Glu Glu Val Ala Glu Gly Ala Leu Ser His Ile
435 440 445
His Ser Leu Ser Val Leu Val Leu Ser His Asn Trp Leu Gln Glu His
450 455 460
Trp Leu Ala Pro Arg Ala Trp Ile His Leu Pro Lys Leu Glu Thr Leu
465 470 475 480
Asp Leu Ser Tyr Asn Arg Leu Val His Val Pro Arg Phe Leu Pro Arg
485 490 495
Gly Leu Arg Arg Leu Thr Leu His His Asp His Ile Glu Arg Ile Pro
500 505 510
Gly Tyr Ala Phe Ala His Met Lys Pro Gly Leu Glu Phe Leu His Leu
515 520 525
Ser His Asn Arg Leu Gln Ala Asp Gly Ile His Ser Val Ser Phe Leu
530 535 540
Gly Leu Arg Ala Ser Leu Ala Glu Leu Leu Leu Asp His Asn Gln Val
545 550 555 560
Gln Ala Ile Pro Arg Gly Leu Leu Gly Leu Lys Gly Leu Gln Val Leu
565 570 575
Gly Leu Ser His Asn Arg Ile Arg Gln Val Pro Leu Asn Ser Ile Cys
580 585 590
Asp Met Arg Val Ala Gln Asp Ser Asn Leu Thr Ser Thr His Leu Glu
595 600 605
Asn Asn Leu Ile Asp Arg Arg Arg Ile Pro Pro Thr Ala Phe Ser Cys

610 615 620
Thr Arg Ala Tyr His Ser Val Val Leu Gln Pro Gln Arg Arg Gly Glu
625 630 635 640
Glu Gly Ser

<210> 55
<211> 653
<212> PRT
<213> Homo sapiens

<400> 55
Met Ala Gly Cys Pro Gly Thr Gly Gln Ser Gly Gln Gln Glu Tyr His
1 5 10 15
Ser Pro Gly Ala His Pro Ala Lys Arg Ser Val Leu Leu Pro Ile Leu
20 25 30
Ala Leu Trp Ala Gly Ser Cys Ser Gly Gly Ala Pro Pro Thr Pro Met
35 40 45
Gly Leu Ala Thr Leu Gln Leu Leu Pro Ser Pro Pro Gly Ala Pro Asp
50 55 60
Gly Gln Leu Gln Pro Ile Pro Gly Ile Gly His Pro Asp Lys Pro Glu
65 70 75 80
Ala Gly Lys Leu Asp Gln Leu Arg Asp Gln Pro Thr Pro Lys Gln Gly
85 90 95
Ala Gln Gly Thr Pro Thr Gln Ser Pro Ser Thr Gly Trp Lys Ala Leu
100 105 110
Pro Arg Pro Gly Leu Ala Leu Arg Lys Glu Ser Pro Pro Val Thr Leu
115 120 125
Glu Gln Glu Gln Gly His Asn Lys Gly Leu Val Ala Glu Trp Ala Gln
130 135 140
Pro Gln Ala Thr Ala Ala Met Arg Ala Gly Ala Gly Lys Pro Glu Ala
145 150 155 160
Leu Lys Leu Arg Pro Trp Gln Ala Gly Arg Asp Pro Gln Ala Gln Glu
165 170 175
Gly Ala Ala Val Thr Glu Glu Asp Gln Gly Gln Arg Thr Gly Gly Arg
180 185 190
Glu Asp Lys Gly Arg Gly Leu Lys Pro Arg Arg Pro Pro Lys Gly Thr
195 200 205
Ser His Gln Pro Gly Leu Arg Ile Arg Arg Pro Gln Lys Asp Arg Ser
210 215 220
Arg Gly Gln Gly Gly Gly Gly Ser Thr Ser Lys Thr Pro Gly His Gly
225 230 235 240
Trp Lys Arg Pro Gly Ser Thr His Gly His Arg His Arg His Ala Asp
245 250 255
Leu Gly Thr Thr Gln Gln Ala Met Pro Ser Leu Pro Ala Ser Cys Leu
260 265 270
Leu Ala Gln Ala Val Ile Ala Cys Gly Asn Val Lys Met Lys His Val
275 280 285
Pro Ala Leu Thr His Pro Gly Leu Thr Thr Leu Tyr Leu Ala Glu Asn
290 295 300
Glu Ile Ala Lys Ile Pro Ala His Thr Phe Leu Gly Leu Pro Asn Leu
305 310 315 320
Glu Trp Leu Asp Leu Ser Lys Asn Lys Leu Asp Pro Arg Gly Leu His
325 330 335
Pro His Ala Phe Lys Asn Leu Met Arg Leu Lys Arg Leu Asn Leu Val
340 345 350
Gly Asn Ser Leu Thr Thr Val Pro Ala Leu Pro Ala Ser Leu Gln Glu
355 360 365
Leu Lys Leu Asn Asp Asn Leu Leu Gln Gly Leu Gln Gly Ser Ser Phe

370 375 380
Arg Gly Leu Ser Gln Leu Leu Thr Leu Glu Val Glu Gly Asn Gln Leu
385 390 395 400
Arg Asp Arg Asp Ile Ser Pro Leu Ala Phe Gln Pro Leu Cys Ser Leu
405 410 415
Leu Tyr Leu Arg Leu Asp Arg Asn Arg Leu Arg Ala Ile Pro Arg Gly
420 425 430
Leu Pro Ser Ser Leu Gln Glu Leu His Leu Gly Thr Asn Leu Ile Glu
435 440 445
Glu Val Ala Glu Gly Ala Leu Ser His Ile His Ser Leu Ser Val Leu
450 455 460
Val Leu Ser His Asn Trp Leu Gln Glu His Trp Leu Ala Pro Arg Ala
465 470 475 480
Trp Ile His Leu Pro Lys Leu Glu Thr Leu Asp Leu Ser Tyr Asn Arg
485 490 495
Leu Val His Val Pro Arg Phe Leu Pro Arg Gly Leu Arg Arg Leu Thr
500 505 510
Leu His His Asp His Ile Glu Arg Ile Pro Gly Tyr Ala Phe Ala His
515 520 525
Met Lys Pro Gly Leu Glu Phe Leu His Leu Ser His Asn Arg Leu Gln
530 535 540
Ala Asp Gly Ile His Ser Val Ser Phe Leu Gly Leu Arg Ala Ser Leu
545 550 555 560
Ala Glu Leu Leu Leu Asp His Asn Gln Val Gln Ala Ile Pro Arg Gly
565 570 575
Leu Leu Gly Leu Lys Gly Leu Gln Val Leu Gly Leu Ser His Asn Arg
580 585 590
Ile Arg Gln Val Pro Leu Asn Ser Ile Cys Asp Met Arg Val Ala Gln
595 600 605
Asp Ser Asn Leu Thr Ser Thr His Leu Glu Asn Asn Leu Ile Asp Arg
610 615 620
Arg Arg Ile Pro Pro Thr Ala Phe Ser Cys Thr Arg Ala Tyr His Ser
625 630 635 640
Val Val Leu Gln Pro Gln Arg Arg Gly Glu Glu Gly Ser
645 650

<210> 56
<211> 305
<212> PRT
<213> Homo sapiens

<400> 56
Met Gly Ala Arg Gly Ala Leu Leu Leu Ala Leu Leu Leu Ala Arg Ala
1 5 10 15
Gly Leu Gly Lys Pro Glu Ser Gln Glu Glu Glu Leu Leu Ser Glu Ala
20 25 30
Cys Gly His Arg Glu Ile His Ala Leu Val Ala Gly Gly Val Glu Ser
35 40 45
Ala Arg Gly Arg Trp Pro Trp Gln Ala Ser Leu Arg Leu Arg Arg Arg
50 55 60
His Arg Cys Gly Gly Ser Leu Leu Ser Arg Arg Trp Val Leu Ser Ala
65 70 75 80
Ala His Cys Phe Gln Lys His Tyr Tyr Pro Ser Glu Trp Thr Val Gln
85 90 95
Leu Gly Glu Leu Thr Ser Arg Pro Thr Pro Trp Asn Leu Arg Ala Tyr
100 105 110
Ser Ser Arg Tyr Lys Val Gln Asp Ile Ile Val Asn Pro Asp Ala Leu
115 120 125
Gly Val Leu Arg Asn Asp Ile Ala Leu Leu Arg Leu Ala Ser Ser Val

130 135 140
Thr Tyr Asn Ala Tyr Ile Gln Pro Ile Cys Ile Glu Ser Ser Thr Phe
145 150 155 160
Asn Phe Val His Arg Pro Asp Cys Trp Val Thr Gly Trp Gly Leu Ile
165 170 175
Ser Pro Ser Gly Thr Pro Leu Pro Pro Pro Tyr Asn Leu Arg Glu Ala
180 185 190
Gln Val Thr Ile Leu Asn Asn Thr Arg Cys Asn Tyr Leu Phe Glu Gln
195 200 205
Pro Ser Ser Arg Ser Met Ile Trp Asp Ser Met Phe Cys Ala Gly Ala
210 215 220
Glu Asp Gly Ser Val Asp Thr Cys Lys Gly Asp Ser Gly Gly Pro Leu
225 230 235 240
Val Cys Asp Lys Asp Gly Leu Trp Tyr Gln Val Gly Ile Val Ser Trp
245 250 255
Gly Met Asp Cys Gly Gln Pro Asn Arg Pro Gly Val Tyr Thr Asn Ile
260 265 270
Ser Val Tyr Phe His Trp Ile Arg Arg Val Met Ser His Ser Thr Pro
275 280 285
Arg Pro Asn Pro Ser Gln Leu Leu Leu Leu Leu Ala Leu Leu Trp Ala
290 295 300
Pro
305

<210> 57
<211> 387
<212> PRT
<213> Homo sapiens

<400> 57
Met Arg Val Thr Trp Asn His Gly Pro Pro Cys Pro Ser Pro Asp Ser
1 5 10 15
Leu Thr Ile Thr Cys Asn Tyr Gly Asn Gly Gly Cys Gln His Ser Cys
20 25 30
Glu Asp Thr Asp Thr Gly Pro Thr Cys Gly Cys His Gln Lys Tyr Ala
35 40 45
Leu His Ser Asp Gly Arg Thr Cys Ile Glu Lys Asp Glu Ala Ala Ile
50 55 60
Glu Arg Ser Gln Phe Asn Ala Thr Ser Val Ala Asp Val Asp Lys Arg
65 70 75 80
Val Lys Arg Arg Leu Leu Met Ala Pro Pro Asp Trp Gly Gln Lys Leu
85 90 95
Gly Leu Phe Gln Leu Gly Ala Pro Pro Gln Gly Thr Ala Gln Gly Leu
100 105 110
Ala Gln Ser Gly Ser Met Glu Ser Leu Leu Ile Asn Leu Val Ile Glu
115 120 125
His Asn Ser Leu Asp Thr Ser Ala Val Leu Val Thr Leu Thr Leu Pro
130 135 140
Cys Pro Asp Ser Val Trp Ser Val Gly Glu Ala Ser Ala His Thr Asp
145 150 155 160
Ser Ala Ala Leu Trp Gly Arg Ser Pro Gly Val Ser Ala Leu Pro Thr
165 170 175
Ser Trp Arg Arg Lys Pro Gly His Gln Arg Val Gln Thr Ser Arg Pro
180 185 190
Arg Arg Leu Ser Arg Pro Pro Gln Val Cys Phe Arg Val Gly Glu Ile
195 200 205
Pro His Glu Ala Ile Met Ser Ala Pro Glu Thr Cys Ala Val Asn Asn
210 215 220
Gly Gly Cys Asp Arg Thr Cys Lys Asp Thr Ala Thr Gly Val Arg Cys

225 230 235 240
Ser Cys Pro Val Gly Phe Thr Leu Gln Pro Asp Gly Lys Thr Cys Lys
245 250 255
Asp Ile Asn Glu Cys Leu Val Asn Asn Gly Gly Cys Asp His Phe Cys
260 265 270
Arg Asn Thr Val Gly Ser Phe Glu Cys Gly Cys Arg Lys Gly Tyr Lys
275 280 285
Leu Leu Thr Asp Glu Arg Thr Cys Gln Asp Ile Asp Glu Cys Ser Phe
290 295 300
Glu Arg Thr Cys Asp His Ile Cys Ile Asn Ser Pro Gly Ser Phe Gln
305 310 315 320
Cys Leu Cys His Arg Gly Tyr Ile Leu Tyr Gly Thr Thr His Cys Gly
325 330 335
Asp Val Asp Glu Cys Ser Met Ser Asn Gly Ser Cys Asp Gln Gly Cys
340 345 350
Val Asn Thr Lys Gly Ser Tyr Glu Cys Val Cys Pro Pro Gly Arg Arg
355 360 365
Leu His Trp Asn Gly Lys Asp Cys Val Gly Arg Gly Ser Leu Leu Leu
370 375 380
Gly Tyr Gly
385

<210> 58
<211> 964
<212> PRT
<213> Homo sapiens

<400> 58
Met Gly Ala Ala Ala Val Arg Trp His Leu Cys Val Leu Leu Ala Leu
1 5 10 15
Gly Thr Arg Gly Arg Leu Ala Gly Gly Ser Gly Leu Pro Gly Ser Val
20 25 30
Asp Val Asp Glu Cys Ser Glu Gly Thr Asp Asp Cys His Ile Asp Ala
35 40 45
Ile Cys Gln Asn Thr Pro Lys Ser Tyr Lys Cys Leu Cys Lys Pro Gly
50 55 60
Tyr Lys Gly Glu Gly Lys Gln Cys Glu Asp Ile Asp Glu Cys Glu Asn
65 70 75 80
Asp Tyr Tyr Asn Gly Gly Cys Val His Glu Cys Ile Asn Ile Pro Gly
85 90 95
Asn Tyr Arg Cys Thr Cys Phe Asp Gly Phe Met Leu Ala His Asp Gly
100 105 110
His Asn Cys Leu Asp Val Asp Glu Cys Gln Asp Asn Asn Gly Gly Cys
115 120 125
Gln Gln Ile Cys Val Asn Ala Met Gly Ser Tyr Glu Cys Gln Cys His
130 135 140
Ser Gly Phe Phe Leu Ser Asp Asn Gln His Thr Cys Ile His Arg Ser
145 150 155 160
Asn Glu Gly Met Asn Cys Met Asn Lys Asp His Gly Cys Ala His Ile
165 170 175
Cys Arg Glu Thr Pro Lys Gly Gly Val Ala Cys Asp Cys Arg Pro Gly
180 185 190
Phe Asp Leu Ala Gln Asn Gln Lys Asp Cys Thr Leu Thr Cys Asn Tyr
195 200 205
Gly Asn Gly Gly Cys Gln His Ser Cys Glu Asp Thr Asp Thr Gly Pro
210 215 220
Thr Cys Gly Cys His Gln Lys Tyr Ala Leu His Ser Asp Gly Arg Thr
225 230 235 240
Cys Ile Glu Thr Cys Ala Val Asn Asn Gly Gly Cys Asp Arg Thr Cys

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                245                     250                     255
Lys Asp Thr Ala Thr Gly Val Arg Cys Ser Cys Pro Val Gly Phe Thr
            260                     265                     270
Leu Gln Pro Asp Gly Lys Thr Cys Lys Asp Ile Asn Glu Cys Leu Val
        275                     280                     285
Asn Asn Gly Gly Cys Asp His Phe Cys Arg Asn Thr Val Gly Ser Phe
    290                     295                     300
Glu Cys Gly Cys Arg Lys Gly Tyr Lys Leu Leu Thr Asp Glu Arg Thr
305                     310                     315                     320
Cys Gln Asp Ile Asp Glu Cys Ser Phe Glu Arg Thr Cys Asp His Ile
                325                     330                     335
Cys Ile Asn Ser Pro Gly Ser Phe Gln Cys Leu Cys His Arg Gly Tyr
            340                     345                     350
Ile Leu Tyr Gly Thr Thr His Cys Gly Asp Val Asp Glu Cys Ser Met
        355                     360                     365
Ser Asn Gly Ser Cys Asp Gln Gly Cys Val Asn Thr Lys Gly Ser Tyr
    370                     375                     380
Glu Cys Val Cys Pro Pro Gly Arg Arg Leu His Trp Asn Gly Lys Asp
385                     390                     395                     400
Cys Val Glu Thr Gly Lys Cys Leu Ser Arg Ala Lys Thr Ser Pro Arg
                405                     410                     415
Ala Gln Leu Ser Cys Ser Lys Ala Gly Gly Val Glu Ser Cys Phe Leu
            420                     425                     430
Ser Cys Pro Ala His Thr Leu Phe Val Pro Asp Ser Glu Asn Ser Tyr
        435                     440                     445
Val Leu Ser Cys Gly Val Pro Gly Pro Gln Gly Lys Ala Leu Gln Lys
    450                     455                     460
Arg Asn Gly Thr Ser Ser Gly Leu Gly Pro Ser Cys Ser Asp Ala Pro
465                     470                     475                     480
Thr Thr Pro Ile Lys Gln Lys Ala Arg Phe Lys Ile Arg Asp Ala Lys
                485                     490                     495
Cys His Leu Arg Pro His Ser Gln Ala Arg Ala Lys Glu Thr Ala Arg
            500                     505                     510
Gln Pro Leu Leu Asp His Cys His Val Thr Phe Val Thr Leu Lys Cys
        515                     520                     525
Asp Ser Ser Lys Lys Arg Arg Arg Gly Arg Lys Ser Pro Ser Lys Glu
    530                     535                     540
Val Ser His Ile Thr Ala Glu Phe Glu Ile Glu Thr Lys Met Glu Glu
545                     550                     555                     560
Ala Ser Asp Thr Cys Glu Ala Asp Cys Leu Arg Lys Arg Ala Glu Gln
                565                     570                     575
Ser Leu Gln Ala Ala Ile Lys Thr Leu Arg Lys Ser Ile Gly Arg Gln
            580                     585                     590
Gln Phe Tyr Val Gln Val Ser Gly Thr Glu Tyr Glu Val Ala Gln Arg
        595                     600                     605
Pro Ala Lys Ala Leu Glu Gly Gln Gly Ala Cys Gly Ala Gly Gln Val
    610                     615                     620
Leu Gln Asp Ser Lys Cys Val Ala Cys Gly Pro Gly Thr His Phe Gly
625                     630                     635                     640
Gly Glu Leu Gly Gln Cys Val Ser Cys Met Pro Gly Thr Tyr Gln Asp
                645                     650                     655
Met Glu Gly Gln Leu Ser Cys Thr Pro Cys Pro Ser Ser Asp Gly Leu
            660                     665                     670
Gly Leu Pro Gly Ala Arg Asn Val Ser Glu Cys Gly Gly Gln Cys Ser
        675                     680                     685
Pro Gly Phe Phe Ser Ala Asp Gly Phe Lys Pro Cys Gln Ala Cys Pro
    690                     695                     700
Val Gly Thr Tyr Gln Pro Glu Pro Gly Arg Thr Gly Cys Phe Pro Cys
705                     710                     715                     720
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Gly Gly Gly Leu Leu Thr Lys His Glu Gly Thr Thr Ser Phe Gln Asp
725 730 735
Cys Glu Ala Lys Val His Cys Ser Pro Gly His His Tyr Asn Thr Thr
740 745 750
Thr His Arg Cys Ile Arg Cys Pro Val Gly Thr Tyr Gln Pro Glu Phe
755 760 765
Gly Gln Asn His Cys Ile Thr Cys Pro Gly Asn Thr Ser Thr Asp Phe
770 775 780
Asp Gly Ser Thr Asn Val Thr His Cys Lys Asn Gln His Cys Gly Gly
785 790 795 800
Glu Leu Gly Asp Tyr Thr Gly Tyr Ile Glu Ser Pro Asn Tyr Pro Gly
805 810 815
Asp Tyr Pro Ala Asn Ala Glu Cys Val Trp His Ile Ala Pro Pro Pro
820 825 830
Lys Arg Arg Ile Leu Ile Val Val Pro Glu Ile Phe Leu Pro Ile Glu
835 840 845
Asp Glu Cys Gly Asp Val Leu Val Met Arg Lys Ser Ala Ser Pro Thr
850 855 860
Ser Ile Thr Thr Tyr Glu Thr Cys Gln Thr Tyr Glu Arg Pro Ile Ala
865 870 875 880
Phe Thr Ser Arg Ser Arg Lys Leu Trp Ile Gln Phe Lys Ser Asn Glu
885 890 895
Gly Asn Ser Gly Lys Gly Phe Gln Val Pro Tyr Val Thr Tyr Asp Gly
900 905 910
Lys Ile His Cys Leu His Gly Pro Leu Cys Thr Ala Gln Ala Gly Pro
915 920 925
Trp Arg His Arg Asp Glu Ser His Val Pro Ala Leu Arg Glu Leu Arg
930 935 940
Pro Gly Arg Tyr Arg Pro Gly Ser Arg Thr Asn Thr Val Arg Gly Gln
945 950 955 960
Ser Gln Thr Gly

<210> 59
<211> 213
<212> PRT
<213> Homo sapiens

<400> 59
Ala Met Val Leu Pro Ser Tyr Ser Lys Ser Glu Gly Gly Ser Leu Leu
1 5 10 15
Asp Ile Tyr Cys Leu Leu Thr Tyr Trp Met Glu Val Val Pro Thr Leu
20 25 30
Leu Ala Glu Thr Lys Ile Pro Ala Thr Asp Val Ala Asp Ala Ser Leu
35 40 45
Asn Glu Cys Ser Ser Thr Glu Arg Lys Gln Asp Val Val Leu Leu Phe
50 55 60
Val Thr Leu Ser His Thr Gln Pro Pro Leu Phe His Leu Pro Tyr Val
65 70 75 80
Gln Lys Pro Leu Ile Ser Asn Val Glu Gln Leu Ile Leu Gly Ile Pro
85 90 95
Gly Gln Asn Arg Arg Glu Ile Gly His Gly Gln Asp Ile Phe Pro Ala
100 105 110
Glu Lys Leu Cys His Leu Gln Asp Arg Lys Val Asn Leu His Arg Ala
115 120 125
Ala Trp Gly Glu Cys Ile Val Ala Pro Lys Thr Leu Ser Phe Ser Tyr
130 135 140
Cys Gln Gly Thr Cys Pro Ala Leu Asn Ser Glu Leu Arg His Ser Ser
145 150 155 160

Phe Glu Cys Tyr Lys Arg Ala Val Pro Thr Cys Pro Trp Leu Phe Gln
165 170 175
Thr Cys Arg Pro Thr Met Val Arg Leu Phe Ser Leu Met Val Gln Asp
180 185 190
Asp Glu His Lys Met Ser Val His Tyr Val Asn Thr Ser Leu Val Glu
195 200 205
Lys Cys Gly Cys Ser
210

<210> 60
<211> 189
<212> PRT
<213> Homo sapiens

<400> 60
Asx Met Glu Val Val Pro Thr Leu Leu Ala Glu Thr Lys Ile Pro Ala
1 5 10 15
Thr Asp Val Ala Asp Ala Ser Leu Asn Glu Cys Ser Ser Thr Glu Arg
20 25 30
Lys Gln Asp Val Val Leu Leu Phe Val Thr Leu Ser His Thr Gln Pro
35 40 45
Pro Leu Phe His Leu Pro Tyr Val Gln Lys Pro Leu Ile Ser Asn Val
50 55 60
Glu Gln Leu Ile Leu Gly Ile Pro Gly Gln Asn Arg Arg Glu Ile Gly
65 70 75 80
His Gly Gln Asp Ile Phe Pro Ala Glu Lys Leu Cys His Leu Gln Asp
85 90 95
Arg Lys Val Asn Leu His Arg Ala Ala Trp Gly Glu Cys Ile Val Ala
100 105 110
Pro Lys Thr Leu Ser Phe Ser Tyr Cys Gln Gly Thr Cys Pro Ala Leu
115 120 125
Asn Ser Glu Leu Arg His Ser Ser Phe Glu Cys Tyr Lys Arg Ala Val
130 135 140
Pro Thr Cys Pro Trp Leu Phe Gln Thr Cys Arg Pro Thr Met Val Arg
145 150 155 160
Leu Phe Ser Leu Met Val Gln Asp Asp Glu His Lys Met Ser Val His
165 170 175
Tyr Val Asn Thr Ser Leu Val Glu Lys Cys Gly Cys Ser
180 185

<210> 61
<211> 740
<212> PRT
<213> Homo sapiens

<400> 61
Met Gly Asp Ser Gly Ala Glu Ala Val Gly Gly Gly Gly Thr Tyr Thr
1 5 10 15
Asp Gly Pro Val Leu Leu Leu Tyr Ala Gly Glu Leu Leu Leu Pro Gln
20 25 30
Glu Thr Thr Val Glu Leu Ser Cys Gly Val Gly Pro Leu Gln Val Ile
35 40 45
Leu Gly Pro Glu Gln Ala Ala Val Leu Asn Cys Ser Leu Gly Ala Ala
50 55 60
Ala Ala Gly Pro Pro Thr Arg Val Thr Trp Ser Lys Asp Gly Asp Thr
65 70 75 80
Leu Leu Glu His Asp His Leu His Leu Leu Pro Asn Gly Ser Leu Trp
85 90 95
Leu Ser Gln Pro Leu Ala Pro Asn Gly Ser Asp Glu Ser Val Pro Glu

100 105 110
Ala Val Gly Val Ile Glu Gly Asn Tyr Ser Cys Leu Ala His Gly Pro
115 120 125
Pro Gly Val Leu Ala Ser Gln Thr Ala Val Val Lys Leu Ala Thr Leu
130 135 140
Ala Asp Phe Ser Leu His Pro Glu Ser Gln Thr Val Glu Glu Asn Gly
145 150 155 160
Thr Ala Arg Phe Glu Cys His Ile Glu Gly Leu Pro Ala Pro Ile Ile
165 170 175
Thr Trp Glu Lys Asp Gln Val Thr Leu Pro Glu Glu Pro Arg Leu Ile
180 185 190
Val Leu Pro Asn Gly Val Leu Gln Ile Leu Asp Val Gln Glu Ser Asp
195 200 205
Ala Gly Pro Tyr Arg Cys Val Ala Thr Asn Ser Ala Arg Gln His Phe
210 215 220
Ser Gln Glu Ala Leu Leu Ser Val Ala His Arg Gly Ser Leu Ala Ser
225 230 235 240
Thr Arg Gly Gln Asp Val Val Ile Val Ala Ala Pro Glu Asn Thr Thr
245 250 255
Val Val Ser Gly Gln Ser Val Val Met Glu Cys Val Ala Ser Ala Asp
260 265 270
Pro Thr Pro Phe Val Ser Trp Val Arg Gln Asp Gly Lys Pro Ile Ser
275 280 285
Thr Asp Val Ile Val Leu Gly Arg Thr Asn Leu Leu Ile Ala Asn Ala
290 295 300
Gln Pro Trp His Ser Gly Val Tyr Val Cys Arg Ala Asn Lys Pro Arg
305 310 315 320
Thr Arg Asp Phe Ala Thr Ala Ala Ala Glu Leu Arg Val Leu Ala Ala
325 330 335
Pro Ala Ile Thr Gln Ala Pro Glu Ala Leu Ser Arg Thr Arg Ala Ser
340 345 350
Thr Ala Arg Phe Val Cys Arg Ala Ser Gly Glu Pro Arg Pro Ala Leu
355 360 365
Arg Trp Leu His Asn Gly Ala Pro Leu Arg Pro Asn Gly Arg Val Lys
370 375 380
Val Gln Gly Gly Gly Gly Ser Leu Val Ile Thr Gln Ile Gly Leu Gln
385 390 395 400
Asp Ala Gly Tyr Tyr Gln Cys Val Ala Glu Asn Ser Ala Gly Met Ala
405 410 415
Cys Ala Ala Ala Ser Leu Ala Val Val Val Arg Glu Gly Leu Pro Ser
420 425 430
Ala Pro Thr Arg Val Thr Ala Thr Pro Leu Ser Ser Ser Ala Val Leu
435 440 445
Val Ala Trp Glu Arg Pro Glu Met His Ser Glu Gln Ile Ile Gly Phe
450 455 460
Ser Leu His Tyr Gln Lys Ala Arg Gly Met Asp Asn Val Glu Tyr Gln
465 470 475 480
Phe Ala Val Asn Asn Asp Thr Thr Glu Leu Gln Val Arg Asp Leu Glu
485 490 495
Pro Asn Thr Asp Tyr Glu Phe Tyr Val Val Ala Tyr Ser Gln Leu Gly
500 505 510
Ala Ser Arg Thr Ser Thr Pro Ala Leu Val His Thr Leu Asp Asp Gly
515 520 525
Arg Ala Ser Glu Leu Ala Val Gly Ser Leu Gly Leu Ser Asn Gly Gln
530 535 540
Val Val Lys Tyr Lys Ile Glu Tyr Gly Leu Gly Lys Glu Asp Gln Ile
545 550 555 560
Phe Ser Thr Glu Val Arg Gly Asn Glu Thr Gln Leu Met Leu Asn Ser
565 570 575

```
Leu Gln Pro Asn Lys Val Tyr Arg Val Arg Ile Ser Ala Gly Thr Ala
            580                 585                 590
Ala Gly Phe Gly Ala Pro Ser Gln Trp Met His His Arg Thr Pro Ser
        595                 600                 605
Met His Asn Gln Ser His Val Pro Phe Ala Pro Ala Glu Leu Lys Val
    610                 615                 620
Gln Ala Lys Met Glu Ser Leu Val Val Ser Trp Gln Pro Pro Pro His
625                 630                 635                 640
Pro Thr Gln Ile Ser Gly Tyr Lys Leu Tyr Trp Arg Glu Val Gly Ala
                645                 650                 655
Glu Glu Glu Ala Asn Gly Asp Arg Leu Pro Gly Gly Arg Gly Asp Gln
            660                 665                 670
Ala Trp Asp Val Gly Pro Val Arg Leu Lys Lys Lys Val Lys Gln Tyr
        675                 680                 685
Glu Leu Thr Gln Leu Val Pro Gly Arg Leu Tyr Glu Val Lys Leu Val
    690                 695                 700
Ala Phe Asn Lys His Glu Asp Gly Tyr Ala Ala Val Trp Lys Gly Lys
705                 710                 715                 720
Thr Glu Lys Ala Pro Ala Pro Gly Glu Gly Gly Gly Gly Arg Arg Arg
                725                 730                 735
Gly Gly Leu Arg
            740

<210> 62
<211> 1250
<212> PRT
<213> Homo sapiens

<400> 62
Met Ala Arg Gly Asp Ala Gly Arg Gly Arg Gly Leu Leu Ala Leu Thr
1               5                   10                  15
Phe Cys Leu Leu Ala Ala Arg Gly Glu Leu Leu Leu Pro Gln Glu Thr
            20                  25                  30
Thr Val Glu Leu Ser Cys Gly Val Gly Pro Leu Gln Val Ile Leu Gly
        35                  40                  45
Pro Glu Gln Ala Ala Val Leu Asn Cys Ser Leu Gly Ala Ala Ala Ala
    50                  55                  60
Gly Pro Pro Thr Arg Val Thr Trp Ser Lys Asp Gly Asp Thr Leu Leu
65                  70                  75                  80
Glu His Asp His Leu His Leu Leu Pro Asn Gly Ser Leu Trp Leu Ser
                85                  90                  95
Gln Pro Leu Ala Pro Asn Gly Ser Asp Glu Ser Val Pro Glu Ala Val
            100                 105                 110
Gly Val Ile Glu Gly Asn Tyr Ser Cys Leu Ala His Gly Pro Leu Gly
        115                 120                 125
Val Leu Ala Ser Gln Thr Ala Val Val Lys Leu Ala Thr Leu Ala Asp
    130                 135                 140
Phe Ser Leu His Pro Glu Ser Gln Thr Val Glu Glu Asn Gly Thr Ala
145                 150                 155                 160
Arg Phe Glu Cys His Ile Glu Gly Leu Pro Ala Pro Ile Ile Thr Trp
                165                 170                 175
Glu Lys Asp Gln Val Thr Leu Pro Glu Glu Pro Arg Leu Ile Val Leu
            180                 185                 190
Pro Asn Gly Val Leu Gln Ile Leu Asp Val Gln Glu Ser Asp Ala Gly
        195                 200                 205
Pro Tyr Arg Cys Val Ala Thr Asn Ser Ala Arg Gln His Phe Ser Gln
    210                 215                 220
Glu Ala Leu Leu Ser Val Ala His Arg Gly Ser Leu Ala Ser Thr Arg
225                 230                 235                 240
```

Gly Gln Asp Val Val Ile Val Ala Ala Pro Glu Asn Thr Thr Val Val
245 250 255

Ser Gly Gln Ser Val Val Met Glu Cys Val Ala Ser Ala Asp Pro Thr
260 265 270

Pro Phe Val Ser Trp Val Arg Gln Asp Gly Lys Pro Ile Ser Thr Asp
275 280 285

Val Ile Val Leu Gly Arg Thr Asn Leu Leu Ile Ala Asn Ala Gln Pro
290 295 300

Trp His Ser Gly Val Tyr Val Cys Arg Ala Asn Lys Pro Arg Thr Arg
305 310 315 320

Asp Phe Ala Thr Ala Ala Ala Glu Leu Arg Val Leu Ala Ala Pro Ala
325 330 335

Ile Thr Gln Ala Pro Glu Ala Leu Ser Arg Thr Arg Ala Ser Thr Ala
340 345 350

Arg Phe Val Cys Arg Ala Ser Gly Glu Pro Arg Pro Ala Leu Arg Trp
355 360 365

Leu His Asn Gly Ala Pro Leu Arg Pro Asn Gly Arg Val Lys Val Gln
370 375 380

Gly Gly Gly Gly Ser Leu Val Ile Thr Gln Ile Gly Leu Gln Asp Ala
385 390 395 400

Gly Tyr Tyr Gln Cys Val Ala Glu Asn Ser Ala Gly Met Ala Cys Ala
405 410 415

Ala Ala Ser Leu Ala Val Val Val Arg Glu Gly Leu Pro Ser Ala Pro
420 425 430

Thr Arg Val Thr Ala Thr Pro Leu Ser Ser Ser Ala Val Leu Val Ala
435 440 445

Trp Glu Arg Pro Glu Met His Ser Glu Gln Ile Ile Gly Phe Ser Leu
450 455 460

His Tyr Gln Lys Ala Arg Gly Met Asp Asn Val Glu Tyr Gln Phe Ala
465 470 475 480

Val Asn Asn Asp Thr Thr Glu Leu Gln Val Arg Asp Leu Glu Pro Asn
485 490 495

Thr Asp Tyr Glu Phe Tyr Val Val Ala Tyr Ser Gln Leu Gly Ala Ser
500 505 510

Arg Thr Ser Thr Pro Ala Leu Val His Thr Leu Asp Asp Val Pro Ser
515 520 525

Ala Ala Pro Gln Leu Ser Leu Ser Ser Pro Asn Pro Ser Asp Ile Arg
530 535 540

Val Ala Trp Leu Pro Leu Pro Pro Ser Leu Ser Asn Gly Gln Val Val
545 550 555 560

Lys Tyr Lys Ile Glu Tyr Gly Leu Gly Lys Glu Asp Gln Ile Phe Ser
565 570 575

Thr Glu Val Arg Gly Asn Glu Thr Gln Leu Met Leu Asn Ser Leu Gln
580 585 590

Pro Asn Lys Val Tyr Arg Val Arg Ile Ser Ala Gly Thr Ala Ala Gly
595 600 605

Phe Gly Ala Pro Ser Gln Trp Met His His Arg Thr Pro Ser Met His
610 615 620

Asn Gln Ser His Val Pro Phe Ala Pro Ala Glu Leu Lys Val Gln Ala
625 630 635 640

Lys Met Glu Ser Leu Val Val Ser Trp Gln Pro Pro Pro His Pro Thr
645 650 655

Gln Ile Ser Gly Tyr Lys Leu Tyr Trp Arg Glu Val Gly Ala Glu Glu
660 665 670

Glu Ala Asn Gly Asp Arg Leu Pro Gly Gly Arg Gly Asp Gln Ala Trp
675 680 685

Asp Val Gly Pro Val Arg Leu Lys Lys Lys Val Lys Gln Tyr Glu Leu
690 695 700

Thr Gln Leu Val Pro Gly Arg Leu Tyr Glu Val Lys Leu Val Ala Phe

705 710 715 720
Asn Lys His Glu Asp Gly Tyr Ala Ala Val Trp Lys Gly Lys Thr Glu
725 730 735
Lys Ala Pro Ala Pro Asp Met Pro Ile Gln Arg Gly Pro Pro Leu Pro
740 745 750
Pro Ala His Val His Ala Glu Ser Asn Ser Ser Thr Ser Ile Trp Leu
755 760 765
Arg Trp Lys Lys Pro Asp Phe Thr Thr Val Lys Ile Val Asn Tyr Thr
770 775 780
Val Arg Phe Ser Pro Trp Gly Leu Arg Asn Ala Ser Leu Val Thr Tyr
785 790 795 800
Tyr Thr Ser Ser Gly Glu Asp Ile Leu Ile Gly Gly Leu Lys Pro Phe
805 810 815
Thr Lys Tyr Glu Phe Ala Val Gln Ser His Gly Val Asp Met Asp Gly
820 825 830
Pro Phe Gly Ser Val Val Glu Arg Ser Thr Leu Pro Asp Arg Pro Ser
835 840 845
Thr Pro Pro Ser Asp Leu Arg Leu Ser Pro Leu Thr Pro Ser Thr Val
850 855 860
Arg Leu His Trp Cys Pro Pro Thr Glu Pro Asn Gly Glu Ile Val Glu
865 870 875 880
Tyr Leu Ile Leu Tyr Ser Ser Asn His Thr Gln Pro Glu His Gln Trp
885 890 895
Thr Leu Leu Thr Thr Gln Gly Asn Ile Phe Ser Ala Glu Val His Gly
900 905 910
Leu Glu Ser Asp Thr Arg Tyr Phe Phe Lys Met Gly Ala Arg Thr Glu
915 920 925
Val Gly Pro Gly Pro Phe Ser Arg Leu Gln Asp Val Ile Thr Leu Gln
930 935 940
Glu Lys Leu Ser Asp Ser Leu Asp Met His Ser Val Thr Gly Ile Ile
945 950 955 960
Val Gly Val Cys Leu Gly Leu Leu Cys Leu Leu Ala Cys Met Cys Ala
965 970 975
Gly Leu Arg Arg Ser Pro His Arg Glu Ser Leu Pro Gly Leu Ser Ser
980 985 990
Thr Ala Thr Pro Gly Asn Pro Ala Leu Tyr Ser Arg Ala Arg Leu Gly
995 1000 1005
Pro Pro Ser Pro Pro Ala Ala His Glu Leu Glu Ser Leu Val His Pro
1010 1015 1020
His Pro Gln Asp Trp Ser Pro Pro Pro Ser Asp Val Glu Asp Arg Ala
1025 1030 1035 1040
Glu Val His Ser Leu Met Gly Gly Gly Val Ser Glu Gly Arg Ser His
1045 1050 1055
Ser Lys Arg Lys Ile Ser Trp Ala Gln Pro Ser Gly Leu Ser Trp Ala
1060 1065 1070
Gly Ser Trp Ala Gly Cys Glu Leu Pro Gln Ala Gly Pro Arg Pro Ala
1075 1080 1085
Leu Thr Arg Ala Leu Leu Pro Pro Ala Gly Thr Gly Gln Thr Leu Leu
1090 1095 1100
Leu Gln Ala Leu Val Tyr Asp Ala Ile Lys Gly Asn Gly Arg Lys Lys
1105 1110 1115 1120
Ser Pro Pro Ala Cys Arg Asn Gln Val Glu Ala Glu Val Ile Val His
1125 1130 1135
Ser Asp Phe Ser Ala Ser Asn Gly Asn Pro Asp Leu His Leu Gln Asp
1140 1145 1150
Leu Glu Pro Glu Asp Pro Leu Pro Pro Glu Ala Pro Asp Leu Ile Ser
1155 1160 1165
Gly Val Gly Asp Pro Gly Gln Gly Ala Ala Trp Leu Asp Arg Glu Leu
1170 1175 1180

Gly Gly Cys Glu Leu Ala Ala Pro Gly Pro Asp Arg Leu Thr Cys Leu
1185 1190 1195 1200
Pro Glu Ala Ala Ser Ala Ser Cys Ser Tyr Pro Asp Leu Gln Pro Gly
1205 1210 1215
Glu Val Leu Glu Glu Thr Pro Gly Asp Ser Cys Gln Leu Lys Ser Pro
1220 1225 1230
Cys Pro Leu Gly Ala Ser Pro Gly Leu Pro Arg Ser Pro Val Ser Ser
1235 1240 1245
Ser Ala
1250

<210> 63
<211> 634
<212> PRT
<213> Homo sapiens

<400> 63
Met Ala Gln Gly Val Leu Trp Ile Leu Leu Gly Leu Leu Leu Trp Ser
1 5 10 15
Asp Pro Gly Thr Ala Ser Leu Pro Leu Leu Met Asp Ser Val Ile Gln
20 25 30
Ala Leu Ala Glu Leu Glu Gln Lys Val Pro Ala Ala Lys Thr Arg His
35 40 45
Thr Ala Ser Ala Trp Leu Met Ser Ala Pro Asn Ser Gly Pro His Asn
50 55 60
Arg Leu Tyr His Phe Leu Leu Gly Ala Trp Ser Leu Asn Ala Thr Glu
65 70 75 80
Leu Asp Pro Cys Pro Leu Ser Pro Glu Leu Leu Gly Leu Thr Lys Glu
85 90 95
Val Ala Arg His Asp Val Arg Glu Gly Lys Glu Tyr Gly Val Val Leu
100 105 110
Ala Pro Asp Gly Ser Thr Val Ala Val Glu Pro Leu Leu Ala Gly Leu
115 120 125
Glu Ala Gly Leu Gln Gly Arg Arg Val Ile Asn Leu Pro Leu Asp Ser
130 135 140
Met Ala Ala Pro Trp Glu Thr Gly Asp Thr Phe Pro Asp Val Val Ala
145 150 155 160
Ile Ala Pro Asp Val Arg Ala Thr Ser Ser Pro Gly Leu Arg Asp Gly
165 170 175
Ser Pro Asp Val Thr Thr Ala Asp Ile Gly Ala Asn Thr Pro Asp Ala
180 185 190
Thr Lys Gly Cys Pro Asp Val Gln Ala Ser Leu Pro Asp Ala Lys Ala
195 200 205
Lys Ser Pro Pro Thr Met Val Asp Ser Leu Leu Ala Val Thr Leu Ala
210 215 220
Gly Asn Leu Gly Leu Thr Phe Leu Arg Gly Ser Gln Thr Gln Ser His
225 230 235 240
Pro Asp Leu Gly Thr Glu Gly Cys Trp Asp Gln Leu Ser Ala Pro Arg
245 250 255
Thr Phe Thr Leu Leu Asp Pro Lys Ala Ser Leu Leu Thr Met Ala Phe
260 265 270
Leu Asn Gly Ala Leu Asp Gly Val Ile Leu Gly Asp Tyr Leu Ser Arg
275 280 285
Thr Pro Glu Pro Arg Pro Ser Leu Ser His Leu Leu Ser Gln Tyr Tyr
290 295 300
Gly Ala Gly Val Ala Arg Asp Pro Gly Phe Arg Ser Asn Phe Arg Arg
305 310 315 320
Gln Asn Gly Ala Ala Leu Thr Ser Ala Ser Ile Leu Ala Gln Gln Val
325 330 335

Trp Gly Thr Leu Val Leu Leu Gln Arg Leu Glu Pro Val His Leu Gln
340 345 350
Leu Gln Cys Met Ser Gln Glu Gln Leu Ala Gln Val Ala Ala Asn Ala
355 360 365
Thr Lys Glu Phe Thr Glu Ala Phe Leu Gly Cys Pro Ala Ile His Pro
370 375 380
Arg Cys Arg Trp Gly Ala Ala Pro Tyr Arg Gly Arg Pro Lys Leu Leu
385 390 395 400
Gln Leu Pro Leu Gly Phe Leu Tyr Val His His Thr Tyr Val Pro Ala
405 410 415
Pro Pro Cys Thr Asp Phe Thr Arg Cys Ala Ala Asn Met Arg Ser Met
420 425 430
Gln Arg Tyr His Gln Asp Thr Gln Gly Trp Gly Asp Ile Gly Tyr Ser
435 440 445
Phe Val Val Gly Ser Asp Gly Tyr Val Tyr Glu Gly Arg Gly Trp His
450 455 460
Trp Val Gly Ala His Thr Leu Gly His Asn Ser Arg Gly Phe Gly Val
465 470 475 480
Ala Ile Val Gly Asn Tyr Thr Ala Ala Leu Pro Thr Glu Ala Ala Leu
485 490 495
Arg Thr Val Arg Asp Thr Leu Pro Ser Cys Ala Val Arg Ala Gly Leu
500 505 510
Leu Arg Pro Asp Tyr Ala Leu Leu Gly His Arg Gln Leu Val Arg Thr
515 520 525
Asp Cys Pro Gly Asp Ala Leu Phe Asp Leu Leu Arg Thr Trp Pro His
530 535 540
Phe Thr Ala Val Ser Leu Arg Ser Leu His Tyr Thr Ala Arg Arg Pro
545 550 555 560
Ser Val Tyr Thr Ser Ser Thr Arg Pro Leu Pro Pro Ala Cys Asn Ser
565 570 575
Cys Ala Arg Thr Ala Ser Ala Arg Pro Pro Thr Ser Arg Arg His Val
580 585 590
Tyr Ser Gly Asn Leu Gly Pro Ala Phe Ala Gly His Ser Ala Gly Asn
595 600 605
Ile Pro Asp Pro Val Thr Ser Ala Tyr Ala Ala Ser Ala Gln Pro Gln
610 615 620
Thr Gln Pro Ala Cys Pro Phe Pro Ser Ser
625 630

<210> 64
<211> 576
<212> PRT
<213> Homo sapiens

<400> 64
Met Ala Gln Gly Val Leu Trp Ile Leu Leu Gly Leu Leu Leu Trp Ser
1 5 10 15
Asp Pro Gly Thr Ala Ser Leu Pro Leu Leu Met Asp Ser Val Ile Gln
20 25 30
Ala Leu Ala Glu Leu Glu Gln Lys Val Pro Ala Ala Lys Thr Arg His
35 40 45
Thr Ala Ser Ala Trp Leu Met Ser Ala Pro Asn Ser Gly Pro His Asn
50 55 60
Arg Leu Tyr His Phe Leu Leu Gly Ala Trp Ser Leu Asn Ala Thr Glu
65 70 75 80
Leu Asp Pro Cys Pro Leu Ser Pro Glu Leu Leu Gly Leu Thr Lys Glu
85 90 95
Val Ala Arg His Asp Val Arg Glu Gly Lys Glu Tyr Gly Val Val Leu
100 105 110

Ala Pro Asp Gly Ser Thr Val Ala Val Glu Pro Leu Leu Ala Gly Leu
115 120 125
Glu Ala Gly Leu Gln Gly Arg Arg Val Ile Asn Leu Pro Leu Asp Ser
130 135 140
Met Ala Ala Pro Trp Glu Thr Gly Asp Thr Phe Pro Asp Val Val Ala
145 150 155 160
Ile Ala Pro Asp Val Arg Ala Thr Ser Ser Pro Gly Leu Arg Asp Gly
165 170 175
Ser Pro Asp Val Thr Thr Ala Asp Ile Gly Ala Asn Thr Pro Asp Ala
180 185 190
Thr Lys Gly Cys Pro Asp Val Gln Ala Ser Leu Pro Asp Ala Lys Ala
195 200 205
Lys Ser Pro Pro Thr Met Val Asp Ser Leu Leu Ala Val Thr Leu Ala
210 215 220
Gly Asn Leu Gly Leu Thr Phe Leu Arg Gly Ser Gln Thr Gln Ser His
225 230 235 240
Pro Asp Leu Gly Thr Glu Gly Cys Trp Asp Gln Leu Ser Ala Pro Arg
245 250 255
Thr Phe Thr Leu Leu Asp Pro Lys Ala Ser Leu Leu Thr Met Ala Phe
260 265 270
Leu Asn Gly Ala Leu Asp Gly Val Ile Leu Gly Asp Tyr Leu Ser Arg
275 280 285
Thr Pro Glu Pro Arg Pro Ser Leu Ser His Leu Leu Ser Gln Tyr Tyr
290 295 300
Gly Ala Gly Val Ala Arg Asp Pro Gly Phe Arg Ser Asn Phe Arg Arg
305 310 315 320
Gln Asn Gly Ala Ala Leu Thr Ser Ala Ser Ile Leu Ala Gln Gln Val
325 330 335
Trp Gly Thr Leu Val Leu Leu Gln Arg Leu Glu Pro Val His Leu Gln
340 345 350
Leu Gln Cys Met Ser Gln Glu Gln Leu Ala Gln Val Ala Ala Asn Ala
355 360 365
Thr Lys Glu Phe Thr Glu Ala Phe Leu Gly Cys Pro Ala Ile His Pro
370 375 380
Arg Cys Arg Trp Gly Ala Ala Pro Tyr Arg Gly Arg Pro Lys Leu Leu
385 390 395 400
Gln Leu Pro Leu Gly Phe Leu Tyr Val His His Thr Tyr Val Pro Ala
405 410 415
Pro Pro Cys Thr Asp Phe Thr Arg Cys Ala Ala Asn Met Arg Ser Met
420 425 430
Gln Arg Tyr His Gln Asp Thr Gln Gly Trp Gly Asp Ile Gly Tyr Ser
435 440 445
Phe Val Val Gly Ser Asp Gly Tyr Val Tyr Glu Gly Arg Gly Trp His
450 455 460
Trp Val Gly Ala His Thr Leu Gly His Asn Ser Arg Gly Phe Gly Val
465 470 475 480
Ala Ile Val Gly Asn Tyr Thr Ala Ala Leu Pro Thr Glu Ala Ala Leu
485 490 495
Arg Thr Val Arg Asp Thr Leu Pro Ser Cys Ala Val Arg Ala Gly Leu
500 505 510
Leu Arg Pro Asp Tyr Ala Leu Leu Gly His Arg Gln Leu Val Arg Thr
515 520 525
Asp Cys Pro Gly Asp Ala Leu Phe Asp Leu Leu Arg Thr Trp Pro His
530 535 540
Phe Thr Ala Thr Val Lys Pro Arg Pro Ala Arg Ser Val Ser Lys Arg
545 550 555 560
Ser Arg Arg Glu Pro Pro Pro Arg Thr Leu Pro Ala Thr Asp Leu Gln
565 570 575

<210> 65
<211> 734
<212> PRT
<213> Homo sapiens

<400> 65
Met Trp Gly Leu Leu Leu Ala Leu Ala Ala Phe Ala Pro Ala Val Gly
1 5 10 15
Pro Ala Leu Gly Ala Pro Arg Asn Ser Val Leu Gly Leu Ala Gln Pro
20 25 30
Gly Thr Thr Lys Val Pro Gly Ser Thr Pro Ala Leu His Ser Ser Pro
35 40 45
Ala Gln Pro Pro Ala Glu Thr Ala Asn Gly Thr Ser Glu Gln His Val
50 55 60
Arg Ile Arg Val Ile Lys Lys Lys Lys Val Ile Met Lys Lys Arg Lys
65 70 75 80
Lys Leu Thr Leu Thr Arg Pro Thr Pro Leu Val Thr Ala Gly Pro Leu
85 90 95
Val Thr Pro Thr Pro Ala Gly Thr Leu Asp Pro Ala Glu Lys Gln Glu
100 105 110
Thr Gly Cys Pro Pro Leu Gly Leu Glu Ser Leu Arg Val Ser Asp Ser
115 120 125
Arg Leu Glu Ala Ser Ser Ser Gln Ser Phe Gly Leu Gly Pro His Arg
130 135 140
Gly Arg Leu Asn Ile Gln Ser Gly Leu Glu Asp Gly Asp Leu Tyr Asp
145 150 155 160
Gly Ala Trp Cys Ala Glu Glu Gln Asp Ala Asp Pro Trp Phe Gln Val
165 170 175
Asp Ala Gly His Pro Thr Arg Phe Ser Gly Val Ile Thr Gln Gly Arg
180 185 190
Asn Ser Val Trp Arg Tyr Asp Trp Val Thr Ser Tyr Lys Val Gln Phe
195 200 205
Ser Asn Asp Ser Arg Thr Trp Trp Gly Ser Arg Asn His Ser Ser Gly
210 215 220
Met Asp Ala Val Phe Pro Ala Asn Ser Asp Pro Glu Thr Pro Val Leu
225 230 235 240
Asn Leu Leu Pro Glu Pro Gln Val Ala Arg Phe Ile Arg Leu Leu Pro
245 250 255
Gln Thr Trp Leu Gln Gly Gly Ala Pro Cys Leu Arg Ala Glu Ile Leu
260 265 270
Ala Cys Pro Val Ser Asp Pro Asn Asp Leu Phe Leu Glu Ala Pro Ala
275 280 285
Ser Gly Ser Ser Asp Pro Leu Asp Phe Gln His His Asn Tyr Lys Ala
290 295 300
Met Arg Lys Leu Met Lys Gln Val Gln Glu Gln Cys Pro Asn Ile Thr
305 310 315 320
Arg Ile Tyr Ser Ile Gly Lys Ser Tyr Gln Gly Leu Lys Leu Tyr Val
325 330 335
Met Glu Met Ser Asp Lys Pro Gly Glu His Glu Leu Gly Glu Pro Glu
340 345 350
Val Arg Tyr Val Ala Gly Met His Gly Asn Glu Ala Leu Gly Arg Glu
355 360 365
Leu Leu Leu Leu Leu Met Gln Phe Leu Cys His Glu Phe Leu Arg Gly
370 375 380
Asn Pro Arg Val Thr Arg Leu Leu Ser Glu Met Arg Ile His Leu Leu
385 390 395 400
Pro Ser Met Asn Pro Asp Gly Tyr Glu Ile Ala Tyr His Arg Gly Ser
405 410 415
Glu Leu Val Gly Trp Ala Glu Gly Arg Trp Asn Asn Gln Ser Ile Asp

```
                420                     425                     430
Leu Asn His Asn Phe Ala Asp Leu Asn Thr Pro Leu Trp Glu Ala Gln
            435                     440                     445
Asp Asp Gly Lys Val Pro His Ile Val Pro Asn His His Leu Pro Leu
    450                     455                     460
Pro Thr Tyr Tyr Thr Leu Pro Asn Ala Thr Val Ala Pro Glu Thr Arg
465                     470                     475                     480
Ala Val Ile Lys Trp Met Lys Arg Ile Pro Phe Val Leu Ser Ala Asn
                485                     490                     495
Leu His Gly Gly Glu Leu Val Val Ser Tyr Pro Phe Asp Met Thr Arg
            500                     505                     510
Thr Pro Trp Ala Ala Arg Glu Leu Thr Pro Thr Pro Asp Asp Ala Val
        515                     520                     525
Phe Arg Trp Leu Ser Thr Val Tyr Ala Gly Ser Asn Leu Ala Met Gln
    530                     535                     540
Asp Thr Ser Arg Arg Pro Cys His Ser Gln Asp Phe Ser Val His Gly
545                     550                     555                     560
Asn Ile Ile Asn Gly Ala Asp Trp His Thr Val Pro Gly Ser Met Asn
                565                     570                     575
Asp Phe Ser Tyr Leu His Thr Asn Cys Phe Glu Val Thr Val Glu Leu
            580                     585                     590
Ser Cys Asp Lys Phe Pro His Glu Asn Glu Leu Pro Gln Glu Trp Glu
        595                     600                     605
Asn Asn Lys Asp Ala Leu Leu Thr Tyr Leu Glu Gln Val Arg Met Gly
    610                     615                     620
Ile Ala Gly Val Val Arg Asp Lys Asp Thr Glu Leu Gly Ile Ala Asp
625                     630                     635                     640
Ala Val Ile Ala Val Asp Gly Ile Asn His Asp Val Thr Thr Ala Trp
                645                     650                     655
Gly Gly Asp Tyr Trp Arg Leu Leu Thr Pro Gly Asp Tyr Met Val Thr
            660                     665                     670
Ala Ser Ala Glu Gly Tyr His Ser Val Thr Arg Asn Cys Arg Val Thr
        675                     680                     685
Phe Glu Glu Gly Pro Phe Pro Cys Asn Phe Val Leu Thr Lys Thr Pro
    690                     695                     700
Lys Gln Arg Leu Arg Glu Leu Leu Ala Ala Gly Ala Lys Val Pro Pro
705                     710                     715                     720
Asp Leu Arg Arg Arg Leu Glu Arg Leu Arg Gly Gln Lys Asp
                725                     730
```

<210> 66
<211> 358
<212> PRT
<213> Homo sapiens

<400> 66

```
Met Pro Glu Asp Val Arg Glu Lys Lys Glu Asn Leu Leu Leu Asn Ser
1               5                   10                  15
Glu Arg Ser Thr Arg Leu Leu Thr Lys Thr Ser His Ser Gln Gly Gly
            20                  25                  30
Asp Gln Ala Leu Ser Lys Ser Thr Gly Ser Pro Thr Glu Lys Leu Ile
        35                  40                  45
Glu Lys Arg Gln Gly Ala Lys Thr Val Phe Asn Lys Phe Ser Asn Met
    50                  55                  60
Asn Trp Pro Val Asp Ile His Pro Leu Asn Lys Ser Leu Val Lys Asp
65                  70                  75                  80
Asn Lys Trp Lys Lys Thr Glu Glu Thr Gln Glu Lys Arg Arg Ser Phe
                85                  90                  95
Leu Gln Glu Phe Cys Lys Lys Tyr Gly Gly Val Ser His His Gln Ser
```

```
            100                     105                     110
His Leu Phe His Thr Val Ser Arg Ile Tyr Val Glu Asp Lys His Lys
        115                     120                     125
Ile Leu Tyr Cys Glu Val Pro Lys Ala Gly Cys Ser Asn Trp Lys Arg
    130                     135                     140
Ile Leu Met Val Leu Asn Gly Leu Ala Ser Ser Ala Tyr Asn Ile Ser
145                     150                     155                     160
His Asn Ala Val His Tyr Gly Lys His Leu Lys Lys Leu Asp Ser Phe
                165                     170                     175
Asp Leu Lys Gly Ile Tyr Thr Arg Leu Asn Thr Tyr Thr Lys Ala Val
            180                     185                     190
Phe Val Arg Asp Pro Met Glu Arg Leu Val Ser Ala Phe Arg Asp Lys
        195                     200                     205
Phe Glu His Pro Asn Ser Tyr Tyr His Pro Val Phe Gly Lys Ala Ile
    210                     215                     220
Ile Lys Lys Tyr Arg Pro Asn Ala Cys Glu Glu Ala Leu Ile Asn Gly
225                     230                     235                     240
Ser Gly Val Lys Phe Lys Glu Phe Ile His Tyr Leu Leu Asp Ser His
                245                     250                     255
Arg Pro Val Gly Met Asp Ile His Trp Glu Lys Val Ser Lys Leu Cys
            260                     265                     270
Tyr Pro Cys Leu Ile Asn Tyr Asp Phe Val Gly Lys Phe Glu Thr Leu
        275                     280                     285
Glu Glu Asp Ala Asn Tyr Phe Leu Gln Met Ile Gly Ala Pro Lys Glu
    290                     295                     300
Leu Lys Phe Pro Asn Phe Lys Asp Arg His Ser Ser Asp Glu Arg Thr
305                     310                     315                     320
Asn Ala Gln Val Val Arg Gln Tyr Leu Lys Asp Leu Thr Arg Thr Glu
                325                     330                     335
Arg Gln Leu Ile Tyr Asp Phe Tyr Tyr Leu Asp Tyr Leu Met Phe Asn
            340                     345                     350
Tyr Thr Thr Pro Phe Leu
        355
```